Responder Analysis – A new method to document a clinically meaningful treatment benefit in nocturia

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Hypothesis/Aim of study

- Reduction in nocturnal voids is the recommended clinical endpoint of nocturia. This has been shown to translate into improved health-related quality of life (HRQoL). But what constitutes a clinically meaningful improvement in voids and quality of life?
- The conventional approach was to establish a minimally important difference (MID), to see whether the average treatment benefit of a medical intervention is higher than this MID threshold. There are a number of ways to evaluate this, based on **group means**
- A recent scientific FDA recommendation is to provide evidence of a clinically meaningful treatment benefit on an **individual basis**. One should conduct responder analyses, as well as present cumulative distribution functions (CDFs). For a nocturia treatment, this translates into four segments:
  - A reduction from baseline of at least 1.2 voids or more per night (somewhat better)
  - A reduction from baseline of at least 1.7 voids or more per night (much better)
  - A reduction to less than 2 voids per night (threshold for bothersome nocturia according to the scientific literature [1])
  - Complete responders, i.e. dry nights or "cured from nocturia"

Methods

- Desmopressin orally disintegrating tablet (ODT) was assessed in two phase 3 double-blind randomised placebo-controlled trials of desmopressin ODT in males (50/75µg; NCT01262456) and females (25µg; NCT01223937) at multiple centers across the US and Canada, on adult subjects with nocturia. Our analyses focused on the Nocturnal Polyuria (NP) sub-population (approx. 90% of the study samples)
- Eligible patients had ≥2 voids per night determined via 3-day frequency-volume chart
- Patients completed the standard Nocturia Quality of Life (N-QoL) questionnaire at monthly visits [2]. N-QoL includes 12 questions with a total score ranging from 0 (low QoL) to 100 (high QoL)
- The logit of the responder probability was adjusted for the baseline number of nocturnal voids as covariate and treatment and age stratum at randomization as factors. The N-QoL total score is adjusted for baseline N-QoL total score

Results

Table 1. Responder analysis of reduction from baseline of at least 1,2 voids and reduction to less than 2 voids per night at Month 3

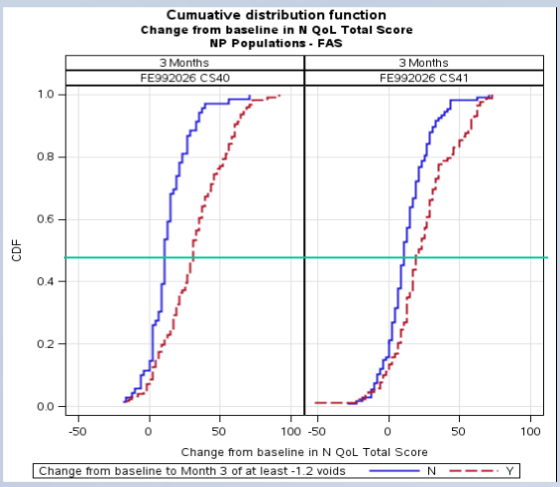
Treatment	Adjusted Responder Probability	Odds ratio	P-value (chi-square test)
	Reduction of at least 1.2 voids / to less than 2 voids		
Women (CS40)			
Desmopressin ODT	75% / 56%	2.33 / 2.06	0.009* / 0.019*
Placebo	56% / 39%		
Men (CS41)			
Desmopressin ODT	59% / 29%	2.66 / 1.75	0.003* / 0.105*
Placebo	35% / 19%		

Note: *At the 3 Month follow-up responders had a reduction of nocturnal voids from baseline that were about 1.5 voids larger than those of the non responders (women -1.57 voids; men -1.59 voids, and women -1.46 voids; men -1.61 voids in the two responder groups respectively, with p<0,001 in all groups)

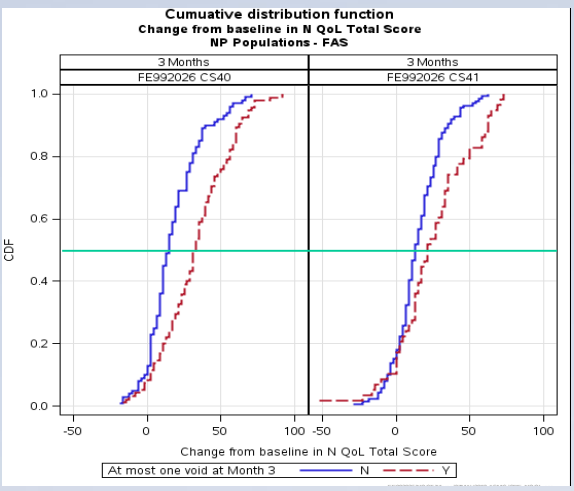
Table 2. Difference between the two responder groups (reduction from baseline of at least 1,2 voids and reduction to less than 2 voids voids per night) in N-QoL total score at Month

Responder Group	Mean change N-QoL	Difference (CI)	P-value (t test)
	Reduction of at least 1.2 voids / to less than 2 voids		
Women (CS40)			
A responder	30.34 / 32.94	15.14 (10.29;20.00) /15.52 (10.98;20.06)	<0.001 for both groups
Not a responder	15.19 / 17.42		
Men (CS41)			
A responder	22.06 / 24.17	8.45 (3.77;13.12) /9.56 (4.51;14.61)	<0.001 for both groups
Not a responder	13.61 / 14.61		

Graph 1: Cumulative distribution function for the mean change from baseline in N-QoL total score – women and men with a reduction from baseline of at least 1.2 voids per night (median in green)



Graph 2: Cumulative distribution function for the mean change green) from baseline in N-QoL total score – women and men with a reduction to less than 2 voids per night (median in green)



Note: The cumulative distribution of change from baseline is included to illustrate responder rates at different thresholds as indicators of a clinically meaningful improvement. Here the Y-axis is the proportion of patients and the X-axis is the change from baseline in N-QoL total score.

Interpretation of Results

- Space only permits a presentation of the responder definition of reduction from baseline of at least 1.2 voids and reduction to less than 2 voids, but the other two definitions present similar results, albeit with fewer patients
- More patients in the desmopressin ODT arms met these responder criteria after 3 months of treatment, as compared to placebo
- The different voiding responder definitions translate into substantial health-related quality of life benefits
- Scientific literature indicates that an N-QoL difference of about 6 points is clinically meaningful [3]

Concluding Message

- This approach allows the audience to assess whether a new treatment generates a clinically meaningful improvement to the patients
- The higher voiding response rates with desmopressin ODT compared to placebo, irrespective of the responder definition, indicate a relevant and clinically important treatment benefit across the NP patient population
- The published literature indicates that the QoL improvement could also be considered clinically meaningful [3]

REFERENCES

1.Tikkinen KA et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol. 2010, **57**:488-96; 2. Abraham L et al. Development and validation of a quality-of-life measure for men with nocturia. Urology. 2004, **63**:481-6; 3. Yu H-J et al.. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology 2006, **67**:713–8.