Testimony Before the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Regarding New Drug Application 022517 for NOCDURNA (desmopressin)

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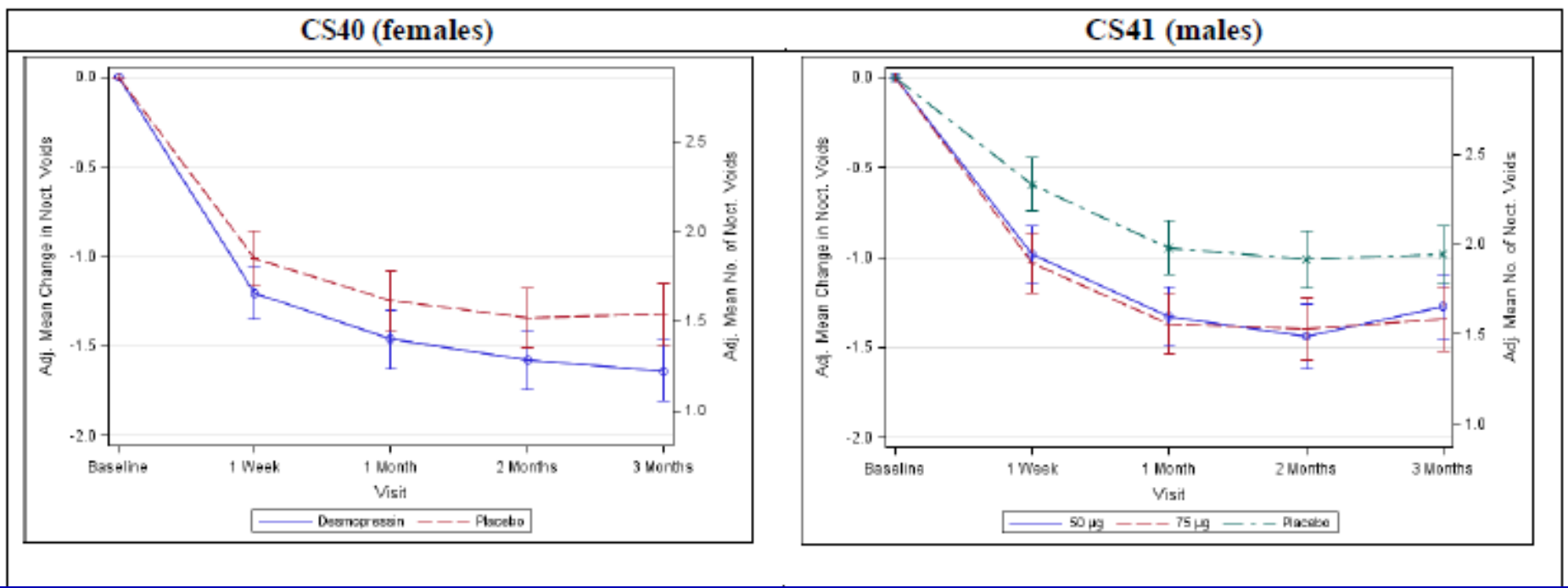
(We have no financial conflicts of interest)

Introduction: Oppose Approval

- We strongly oppose FDA approval of Nocdurna (desmopressin) — a drug already twice rejected by the FDA — for treatment of nocturia because the drug:
  - offers meager clinically meaningful benefit relative to placebo for the proposed indication; and
  - causes severe, potentially life-threatening hyponatremia, a risk that far outweighs the drug's benefits.

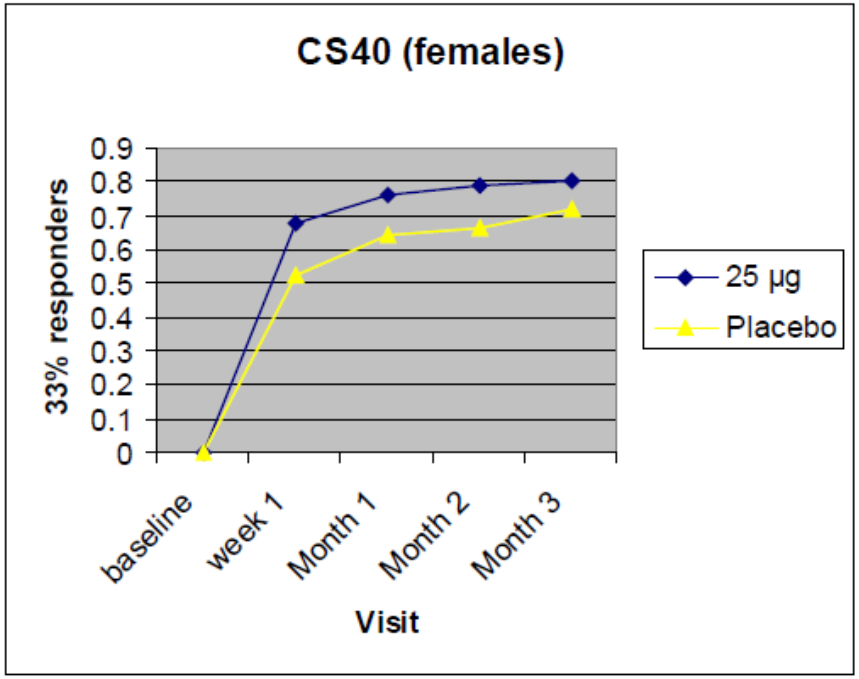
Efficacy Assessment: Meager Clinical Benefit

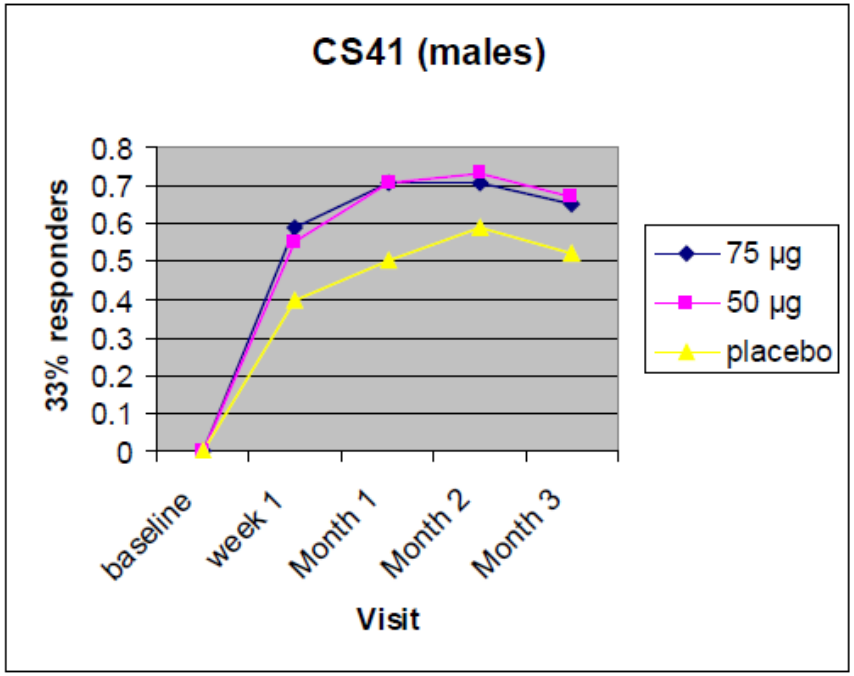
Adjusted Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Voids (Trials CS40 and CS41)



Efficacy Assessment: Meager Clinical Benefit

Proportion of 33% Responders by Visit (Trials CS40 and CS41)





Efficacy Assessment: Meager Clinical Benefit

The FDA's Division of Metabolic and Endocrine Products' conclusions regarding the efficacy results from trials CS40 and CS41:

- **"[R]elative to placebo, the treatment effect size associated with Nocdurna in the currently studied patient population with nocturia was modest and of unclear benefit."** **[Emphasis added]**
- **"The Nocdurna clinical program did not provide convincing evidence of clinical benefit beyond the above mentioned reduction in nocturnal voids."**

Efficacy Assessment: Meager Clinical Benefit

The FDA's Division of Bone, Reproductive and Urologic Products' assessment of the efficacy data for Nocdurna:

- **"The demonstrated effect of NOCDURNA on the frequency of nocturia in patients with nocturnal polyuria is small when compared to placebo. The clinical meaningfulness of this small effect is not interpretable in the absence of a validated measure of the clinical benefit of reduction of nocturia episodes." [Emphasis added]**

Efficacy Assessment: Meager Clinical Benefit

FDA Study Endpoints Consult Review assessing the data on quality of life measures concluded:

- **"[T]he clinical trial evidence submitted by the applicant is inadequate to support labeling claims on the basis of the [Nocturia Impact Diary] or [Nocturia Quality-of-Life questionnaire] because of the exploratory nature of the data. Therefore, these clinical trial results do not meet standards for inclusion in labeling claims." [Emphasis added]**

Efficacy Assessment: Meager Clinical Benefit

Reviewer with the FDA's Division of Psychiatry Products noted the following regarding the sleep data:

- **"It is important to note that the sponsor's submission does not provide new clinical trial data. Rather, the sponsor provides post-hoc analyses of existing trial data in the context of selected literature, ostensibly contributing additional "benefit" considerations to the benefit-risk evaluation." [Emphasis added]**

Efficacy Assessment: Meager Clinical Benefit

Reviewer with the FDA's Division of Psychiatry Products concluded the following regarding the sleep data:

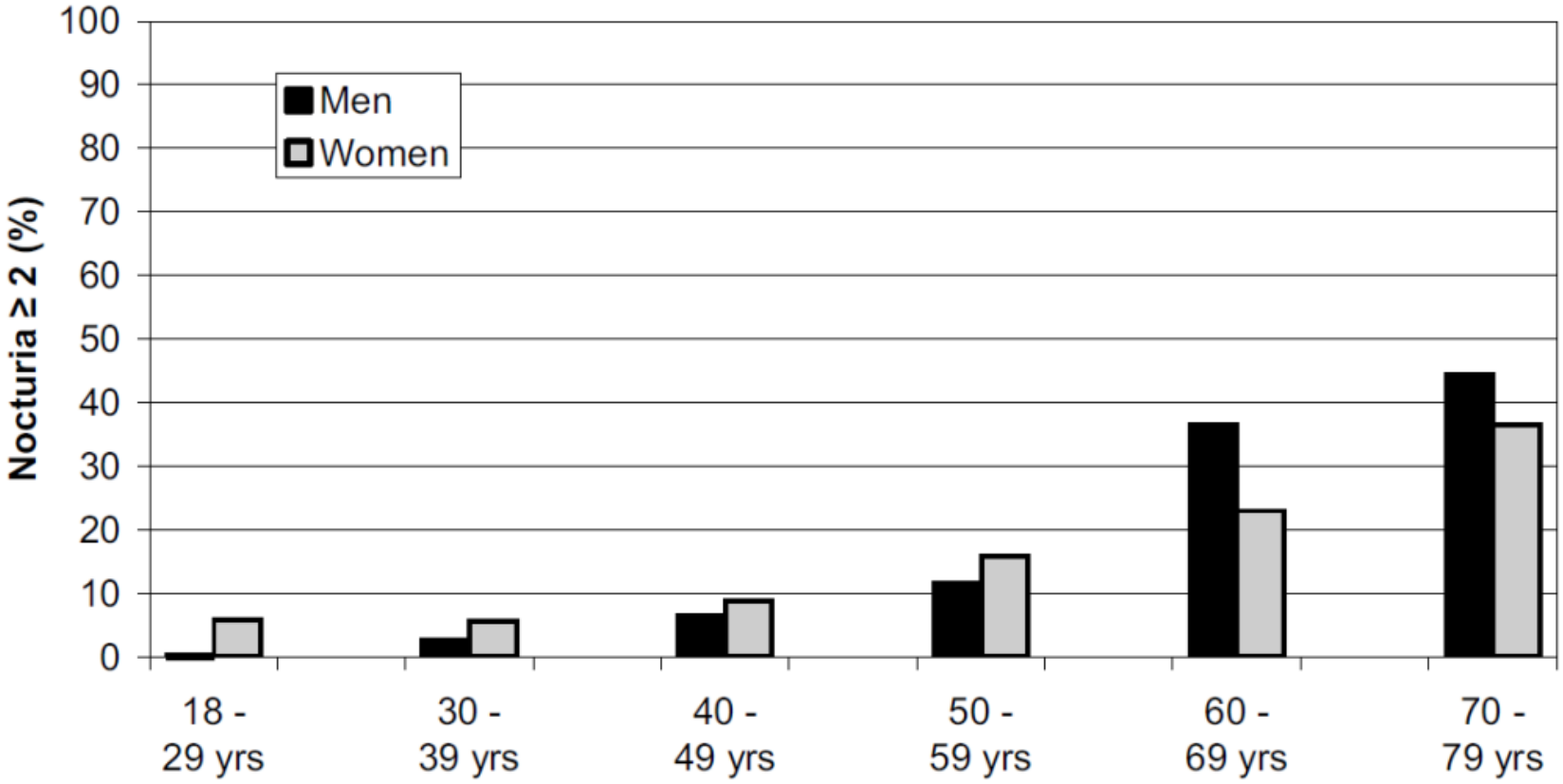
- **"Although there is some face validity to the sponsor's argument that a placebo-subtracted increase of 39-49 minutes in FUSP [first uninterrupted sleep period] may improve health-related quality of life, the means by which that conclusion is reached requires several inferential steps, each based on limited direct evidence. The sponsor is making an argument based on a proxy in the absence of objective evidence." [Emphasis added]**

Major Risk: Severe Hyponatremia

- Desmopressin, given its mechanism of action in blocking water excretion by the kidneys, has long been known to cause acute hyponatremia.
- Acute severe hyponatremia is a medical emergency because it can cause cerebral edema, which can result in loss of consciousness, seizure, coma, respiratory arrest, and death.
- In addition, FDA reviewers noted that mild chronic hyponatremia may be associated with neurocognitive impairment, gait disturbances and predisposition to falls, osteoporosis and fractures in elderly patients.

Major Risk: Severe Hyponatremia

Prevalence of Nocturia by Age and Sex



Major Risk: Severe Hyponatremia

- The sponsor's proposed monitoring plan is not sufficient to mitigate the risk of hyponatremia because the absence of hyponatremia during the initial month of treatment fails to guarantee that patients will not develop hyponatremia during later chronic use.
- Many patients without hyponatremia during the first month of Nocdurna use will develop any number of factors predisposing to hyponatremia at a later time — such as renal impairment, heart failure, or new concomitant use of prescription and over-the counter NSAIDs or other drugs — which could lead to acute severe hyponatremia when combined with long-term Nocdurna use.

Major Risk: Severe Hyponatremia

The FDA correctly noted that:

> **"[A]lthough the risk of severe hyponatremia has been reduced considerably once the Nocdurna doses have been reduced in both males and females[,] there is still a persistent risk for hyponatremia which may become more apparent if the drug is used in a larger and more diverse population with additional comorbidities and risk factors under clinical practice conditions that differ considerably from the relatively controlled environment of a clinical trial." [Emphasis added]**

Conclusion

- Given the meager clinical benefit of Nocdurna seen in the pivotal clinical trials, no risk mitigation strategy will reduce the risk of severe hyponatremia sufficient to make the case that the benefits outweigh the risks of this drug.
- In the interest of protecting public health, we urge the committee to recommend that the FDA reaffirm its prior decision and not approve Nocdurna.