indication of a more severe level of ED, or a disappointing experience with the drug in the past. The small sample size ($n=7$) should be taken into consideration as well.

For the mean six-point SEP score (primary efficacy variable) there was a period effect, which means that patients did increasingly better as the trial periods advanced, independent of the type of treatment.

The observed period effect across all four treatments in the study is most likely due to increased confidence with sexual performance during study participation.

Despite the recognition bias, the four-way, randomized cross-over design allowed for a more accurate determination of treatment preference than a parallel design. Those patients who completed all four study periods were about equally divided over their treatment preference.

Most AE were mild in severity, and the most frequently reported AE, rhinitis and headache, were to be expected based on the pharmacology of these agents.

The results of this study show that there may be a maximum level that single or a combination of vasoactive drugs can achieve in the treatment of ED. This is supported by the observation that the triple drug combination performed as well as the two combinations of apomorphine plus phentolamine, and of phentolamine plus papaverine. However, the triple combination showed more AE than the other treatments.

Coupled with the relative safety of the bi-combo formulations, one can conclude that an oral combination of two vasoactive drugs with different pharmacodynamic activity may provide an alternative approach to oral treatment with the highest approved dose of sildenafil. Especially, the combination of phentolamine and apomorphine warrants further clinical investigation.

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Editorial Comment

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Apomorphine acts on central dopamine receptors and enhances signals in supraspinal neuronal pathways, which are involved in the regulation of penile erection, and can hereby improve an otherwise subnormal erectile response. In the management of erectile dysfunction, apomorphine is approved and clinically used by sublingual administration. In the recommended dose-range, this route of

administration of apomorphine avoids first pass hepatic metabolism and ensures rapid therapeutic concentrations, with a low frequency of side effects. With the sublingual preparation, the recommended starting dose of apomorphine should be 2 mg, which can be clinically effective in producing satisfactory erections with minimal side effects. If necessary, the apomorphine dose can be increased to 3 mg. At 3 mg of apomorphine (irrespective of severity of ED), a roughly 20–30% increase in attempts resulting in satisfactory erections, ie erections firm enough for intercourse, compared to placebo have been reported.[1,2] At this dose, common adverse effects include headache and nausea (3–7%). Adverse effects have also been reported to decline by 'optimizing' the dosage, ie by starting at a lower dose of apomorphine (2 mg), or by repeated use of the compound. A dose of 4 mg of apomorphine did not further improve erectile responses but increased the occurrence of headache and nausea (6–14%).[1,2] Use of higher doses than recommended increases the risk of more adverse events such as transient hypotension

When combining apomorphine with peripherally vasoactive drugs on an experimental or clinical trial basis, circulatory side effects must be taken into careful consideration. The main aim of such combinations would be to obtain better efficacy and to diminish side effects by reducing the dose or preferably by increasing the selectivity for the target structure of the respective agent. By oral route (ingestion), instead of sublingual administration, first-pass hepatic metabolism of apomorphine is extensive and bioavailabilty of the drug is low.

P Hedlund

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Response to Editorial Comment

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Based on available data on sublingual apomorphine (Uprima®) and on personal communication with leading experts in the field of ED treatment, 4 mg or more of SL apomorphine may be needed in the majority of patients to induce an adequate response. At these dose levels, however, side effects and patient tolerance become an important issue.

Zonagen has gathered, in the past years, a wealth of information on the efficacy and safety of both the 40 mg and 80 mg dose of phentolamine (Vasomax®) in the treatment of ED. Although Vasomax® was shown to be efficacious and well tolerated, the percentage of patients that improved with treatment was not as high as that observed with sildenafil citrate (Viagra®). Also, studies showed that not all patients treated with Viagra® respond favourably to the drug, or may discontinue the drug due to side effects associated with PDE5 inhibitors.

Based on this information our Company decided that, in order to further improve efficacy while still maintaining adequate and acceptable safety profiles, combination therapies would have to be studied.

This Phase IIa exploratory study was conducted after Zonagen had conducted an initial Phase I safety study in which we compared the safety and pharmacokinetics (PK) of different combinations of phentolamine and apomorphine. The different combinations of 40 mg phentolamine with 2, 4, or 6 mg oral apomorphine were very well tolerated, and hopefully this adequately addresses Dr Hedlund's concern about the potential for circulatory side effects when combining these two active compounds.

The PK profile of the 6 mg combination showed a plasma concentration versus time curve for oral apomorphine that fell exactly in between those published for the 2 mg and 4 mg dose of SL apomorphine. Therefore, I agree with Dr Hedlund's statement that the bioavailablity of orally administered apomorphine is lower than of SL apomorphine. However, this may in fact be beneficial since the fast rise in blood levels of apomorphine after administration of the SL formulations may be responsible for some of the side effects observed with this type of formulation.

The current study shows that a) combinations of orally active compounds should be considered when designing new, inexpensive therapies for ED which will increase efficacy over some existing mono-therapies, and b) that a combination of phentolamine and oral apomorphine is well tolerated and did not induce potentially serious circulatory side effects.

P Lammers