value to improving sleep in a patient with insomnia by inducing narcolepsy symptoms.

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COMPETING INTERESTS STATEMENT
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**Brisbare-Roch *et al.* reply:**

We agree with Tafti that animal and human orexin deficiency syndromes suggest a theoretical risk of cataplexy following administration of an orexin receptor antagonist. Our study involved healthy rodent, canine and human subjects, in whom a dual $OX_1/OX_2$ receptor antagonist that crosses the blood-brain barrier elicited somnolence and sleep, but not cataplexy, when administered as a single oral dose during the active period of the circadian cycle[1]. The absence of cataplexy in all three species was in contrast to the narcolepsy-cataplexy syndromes commonly observed in rodents, canines and humans. Thus it appears that the impact of acute and transient pharmacological antagonism of $OX_1$ and $OX_2$ receptors differs from that of a chronic and life-long deactivation induced by genetic or acquired orexin peptide or orexin receptor deficits. Our observations confirm those from other studies, and suggest that somnolence and cataplexy might be separable phenomena and that orexin deficit per se is not sufficient to cause cataplexy. Some narcoleptic patients do not develop cataplexy despite low CSF orexins[2,3], and loss of hypothalamic factors besides orexins, such as neuronal activity–regulated pentraxin (Narp), dynorphin and glutamate, possibly contributes to the narcolepsy syndrome[4–6]. Many additional variables may have contributed to the occurrence of somnolence without cataplexy that we observed: the dosage, the degree of receptor antagonism, the relative inhibition at $OX_1$ and $OX_2$ receptors, and the duration of orexin receptor blockade.

Concerning our experimental approaches, we are of the opinion that the methods described in our article, in particular for assessing the presence of cataplexy, fully allow the conclusions drawn. We also do not consider it critically important to demonstrate that our drug blocks the effects of exogenously administered orexins. Such experiments serve only to recapitulate agonist-antagonist interactions already demonstrated *in vitro*. Our goal, rather, was to assess the impact of our compound on endogenous orexins and the maintenance of wakefulness.

Tafti states that ACT-078573 treatment of rats primarily decreased their locomotor activity during wakefulness, rather than inducing sleep. Our EEG data showed that waking time decreased in proportion to increased time in NREM sleep and shortened latency to NREM sleep; together with increased REM sleep time, this resulted in a net decrease in home cage activity. Our assessment of a physiological sleep pattern is based on the increase in both NREM and REM sleep observed with ACT-078573 (**Table 1**). The behavioral assessment of sleep posture in dogs is a *prima facie* assessment of sleep and the distal muscle movements a surrogate of REM activity. Since the publication of our manuscript, we have reported early proof of concept for enhanced sleep efficiency following ACT-078573 administration at bedtime in patients with primary insomnia (www.actelion.com/uninet/www/www_main_p.nsf/Content/me+04+Feb+2007).

**Table 1 Relative proportions of NREM and REM sleep in rats**

| Rat EEG/EMG | Vehicle[1] | ACT-078573[1] | Zolpidem[1] |
|---|---|---|---|
| NREM sleep | 33.7% of 12-h night (243 min) | 39.7% of 12-h night (286 min) | 39.6% of 12-h night (285 min) |
| REM sleep | 4.6% of 12-h night; 12% of total sleep time (33 min) | 6.9% of 12-h night; 15% of total sleep time (50 min) | 2.5% of 12-h night; 6% of total sleep time (17 min) |

[1]Vehicle, ACT-078573 and zolpidem were administered orally (100 mg per kg body weight).

Tafti wonders why only two 25-min EEG recording periods were performed in the entry-into-man study. The duration and timing of EEG recording were chosen to accommodate the purposes of this phase I study, which were to assess the drug's safety, tolerability and pharmacokinetics in healthy subjects. This is also a variant of a multiple sleep latency test (MSLT) that is used as a diagnostic tool to assess sleep-onset REM periods (SOREMP) in narcoleptic patients[3]. Full EEG evaluations are being and will be conducted in dedicated clinical trials, and will be published in due course. Finally, Tafti worries about short latency to sleep stage 2. First, short latency is not uncommon in healthy subjects[7], as also evidenced in the placebo controls; second, the latency was shortened dose dependently, and we have no reason to believe that a shortened latency to stage 2 is undesirable.

As this discussion indicates, there are still many open questions related to the effects of an orexin receptor antagonist, and in that sense our study can be considered as initial but essential groundwork. Our selective, dual $OX_1/OX_2$ receptor antagonist is a useful agent for delineating the physiological and pathophysiological roles of endogenous orexins. We view the results of our proof-of-concept study with ACT-078573 as very promising and reinforcing the results described in our paper. The increase in both NREM and REM sleep with ACT-078573 may mimic a physiological sleep pattern better than the increase in only NREM sleep induced by previous hypnotic drugs. However, many more studies are needed before we can conclude whether dual orexin receptor antagonists will represent a safer and better class of sleep-promoting agents than currently available hypnotic drugs.

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