

RELATIONSHIP OF SUBJECTIVE AND OBJECTIVE ENDPOINTS FOR OUTCOMES OF A PHASE I TRIAL OF A POTENTIAL NEW SLEEP AGENT

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INTRODUCTION

The study of the pharmacokinetic/pharmacodynamic relationship of hypnotic drugs for insomnia has difficult methodological and practical issues, such as blood sampling, sleep fragmentation or choices of pharmacodynamic endpoints that reliably reflect the time course of hypnotic activity during the night. In a phase I placebo-controlled, crossover double-blind study we employed objective and subjective measures to fully investigate the effects of three novel formulations of zaleplon 15 mg on the central nervous system. The differences in release characteristics were provided by the Geoclock® (SkyePharma, London, UK) delivery system, a unique technology that allows delivery of a drug over a preset time period. The objective measures used were 4-lead electroencephalography (EEG), Multiple Sleep Latency Test (MSLT) and the Karolinska Drowsiness Test (KDT). The Karolinska Sleepiness Scale (KSS) was the subjective measure.

OBJECTIVE

To study the relationship between the pharmacokinetic and pharmacodynamic profiles of three novel zaleplon formulations and compare the pharmacodynamic results as defined by subjective and objective measurements.

METHODS

- Study design: Phase I, double-blind, crossover, placebo- and open-labeled marketed immediate-release zaleplon (10 mg) controlled single-center study. Crossover administrations of study drugs were separated by a 4- to 7-day washout.
- Participants: 19 healthy volunteers (13 woman, 6 men; ages 21-46 years) were enrolled. None of them presented a sleep disorder or disturbed sleep/wake patterns. Concomitant treatment was not allowed during the study and subjects had to withdraw for any medication within 2 weeks prior to admission (except paracetamol up to 3 g/day). The consumption of alcohol, tobacco, xanthine-containing drinks or caffeine was prohibited during the study.
- Treatments: Single oral doses of zaleplon 15 mg in formulations A, B, and C with different release characteristics, commercially-available 10 mg immediate-release zaleplon and placebo were administered according to a randomized 5-way crossover design. Study drugs were administered at 9:00 AM (± 15 min) after which subjects remained in bed under the supervision of the clinical staff for 12 hours.
- All the tests were performed -20, -12, and -1 hours pre-dose (these three measurements provided baseline) and each hour post-dose for 12 hours. Plasma drug levels were determined -1h predose, and at T_0+30 min, T_0+1 h, $T_0+1.5$ h, T_0+2 h, $T_0+2.5$ h, T_0+3 h, $T_0+3.5$ h, T_0+4 h, T_0+5 h, T_0+6 h, T_0+8 h, T_0+10 h, and T_0+12 h after study drug administration.
- EEG parameters were calculated on the median of the 4 lead couples (F4-T4, F3-T3, T4-O2, T3-O1). Spectral analysis was done to obtain absolute powers of beta, alpha, theta, delta and a sensitive measure for arousal: the alpha-slow-wave index (ASI), defined as [alpha power/(delta + theta powers)].
- For the KDT, delta, theta, alpha and beta powers were calculated from 3-lead pairs (Fz-Cz, Cz-Pz, Pz-Oz) during eyes-open and eyes-closed, and an alpha attenuation coefficient (AAC; eyes-closed alpha power/eyes-open alpha power) was determined.
- The MSLT determines daytime sleepiness by objectively measuring the time from the start of a daytime nap period to the first signs of sleep.
- The KSS is a self rating scale assessing subjective sleepiness. The volunteer is asked to choose between nine different descriptions (1= very alert to 9 = very sleepy, great effort to keep awake, fighting sleep) to indicate sleepiness.
- Differences between each 15 mg formulation and placebo or immediate-release zaleplon 10 mg were studied with a mixed model on change from baseline values to determine whether the treatment affects the pharmacodynamic assessments and whether there is an interaction between treatment effect and time effect.

RESULTS

- A significant main treatment effect was reported for most pharmacodynamic endpoints.
- Between-treatment global contrasts analyses indicate that when all time points are considered together, the three formulations significantly differed from placebo with both objective and subjective measures for hypovigilance and sleepiness.
- Results are summarized in Table 1
- Among the 9 parameters shown in Table 1, only three significant treatment x time interactions were observed between two objective 4-lead EEG parameters (ASI and alpha absolute power), and the subjective KSS. Consequently, time courses of the pharmacodynamic effects were examined on these three variables. Results are shown in Table 2 in relation to zaleplon plasma concentrations.
- A relationship was demonstrated between zaleplon plasma concentration and drug-related pharmacodynamic effects, with peak activity 4-5 hours postdose.

Table 1. Summary of pharmacodynamic results comparing the formulations to placebo global contrasts analyses for parameters showing a significant main treatment effect. Arrows indicate the significance and direction of change compared to placebo induced by the prototype ($\downarrow = p < 0.05$, $\downarrow\downarrow = p < 0.01$, $\downarrow\downarrow\downarrow = p < 0.001$)

Electrophysiological or psychometric assessments		Formulations vs placebo contrasts		
		Formulation A	Formulation B	Formulation C
4-lead EEG	Alpha absolute power	$\downarrow\downarrow\downarrow$	\leftrightarrow	\leftrightarrow
	Alpha Slow Wave Index	$\downarrow\downarrow\downarrow$	\leftrightarrow	$\downarrow\downarrow$
KDT	Eyes-closed Fz-Cz absolute delta power	$\downarrow\downarrow\downarrow$	\leftrightarrow	\downarrow
	Eyes-closed Fz-Cz absolute theta power	\leftrightarrow	$\downarrow\downarrow$	$\downarrow\downarrow$
	Eyes-closed Pz-Oz absolute alpha power	$\downarrow\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow\downarrow$
	Eyes-open Pz-Oz absolute alpha power	$\downarrow\downarrow\downarrow$	\leftrightarrow	\leftrightarrow
	AAC	$\downarrow\downarrow\downarrow$	\downarrow	\downarrow
MSLT		$\downarrow\downarrow\downarrow$	$\downarrow\downarrow$	\downarrow
KSS		$\uparrow\uparrow\uparrow$	\uparrow	\uparrow

Table 2. Time course of the significant pharmacodynamic effects for objective (ASI and alpha power [AP]) and subjective (KSS) measurements in relation to zaleplon concentrations. Stars indicate the significant drug to placebo contrasts (* = $p < 0.05$, ** = $p < 0.01$, * = $p < 0.001$).**

Time	Formulation A			Formulation B			Formulation C			Marketed zaleplon (10 mg)		
	KSS	ASI	AP	KSS	ASI	AP	KSS	ASI	AP	KSS	ASI	AP
T_0+1 h										***	*	*
T_0+2 h	**							*		***		
T_0+3 h	*				*	**				**		
T_0+4 h	***	***	***	*	*	***		*	*			
T_0+5 h	***	***	***		*	*		**	**			
T_0+6 h	*			*								
T_0+7 h	*			*								
T_0+8 h												
T_0+9 h												
T_0+10 h												
T_0+11 h												
T_0+12 h												

Plasma zaleplon color code: undetectable (white), < 5 ng/ml (purple), 5-10 ng/ml (yellow), 10-20 ng/ml (green), > 20 ng/ml (blue)

CONCLUSION

- The pharmacodynamic profile of the three novel formulations was related to the pharmacokinetic profile.
- This study suggests that the pharmacodynamic parameters used in non-insomniac healthy subjects with a morning administration can be useful to characterize the pharmacodynamic profile of new hypnotics and to define a clear pharmacokinetic/pharmacodynamic relationship, which may be difficult to achieve in insomniac patients and polysomnography studies.

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KDT	Eyes-closed Fz-Cz absolute delta power	↓↓↓	↔	↓
	Eyes-closed Fz-Cz absolute theta power	↔	↓↓	↓↓
	Eyes-closed Pz-Oz absolute alpha power	↓↓↓	↓↓	↓↓↓
	Eyes-open Pz-Oz absolute alpha power	↓↓↓	↔	↔
	AAC	↓↓↓	↓	↓
MSLT		↓↓↓	↓↓	↓
KSS		↑↑↑	↑	↑

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T ₀ +2h	**							*		***		
T ₀ +3h	*				*	**				**		
T ₀ +4h	***	***	***	*	*	***		*	*			
T ₀ +5h	***	***	***			*		**	**			
T ₀ +6h	*			*								
T ₀ +7h	*			*								
T ₀ +8h												
T ₀ +9h												
T ₀ +10h												
T ₀ +11h												
T ₀ +12h												
Plasma zaleplon color code			undetectable	< 5 ng/ml	5-10 ng/ml	10-20 ng/ml	> 20 ng/ml					

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