Drugs of the Future 2009, 34(1): 5-10

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.1.1324392



# ALMOREXANT

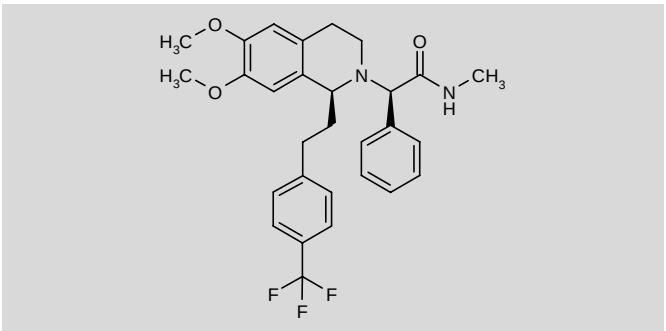
Rec INN

*Dual Orexin $OX_1$/$OX_2$ Antagonist*
*Treatment of Sleep Disorders*

## ACT-078573

2(*R*)-[6,7-Dimethoxy-1(*S*)-[2-[4-(trifluoromethyl)phenyl]ethyl]-1,2,3,4-tetrahydroisoquinolin-2-yl]-*N*-methyl-2-phenylacetamide

InChI=1/C29H31F3N2O3/c1-33-28(35)27(20-7-5-4-6-8-20)34-16-15-21-17-25(36-2)26(37-3)18-23(21)24(34)14-11-19-9-12-22(13-10-19)29(30,31)32/h4-10,12-13,17-18,24,27H,11,14-16H2,1-3H3,(H,33,35)/t24-,27+/m0/s1



$C_{29}H_{31}F_3N_2O_3$
Mol wt: 512.5632
CAS: 871224-64-5
CAS: 871224-62-3 (racemate)
CAS: 913358-93-7 (hydrochloride)
EN: 415452

**ABSTRACT**

*Almorexant is a novel, selective, orally active dual orexin $OX_1$ and $OX_2$ receptor antagonist. It is rapidly absorbed and distributed and shows no tendency to accumulate with repeated dosing. Preclinical studies in rats and dogs have demonstrated a sleep-promoting effect which resembles physiological sleep; this could be quickly reversed upon sensorimotor stimulation and yet allow resumption of sleep upon its cessation. Almorexant's sleep-promoting effects were confirmed in volunteers and patients with primary insomnia. It dose-dependently increased sleep efficiency and decreased sleep latency and wake time after sleep onset. The compound was well tolerated, with no significant effects on next-day motor performance, memory or reaction time.*

**SYNTHESIS**

Condensation of 3,4-dimethoxyphenethylamine (I) with 4-(trifluoromethyl)hydrocinnamic acid (II) in refluxing toluene affords amide (III), which undergoes Bischler–Napieralski cyclization to the dihydroisoquinoline (IV) upon treatment with $POCl_3$ in acetonitrile. Alternatively, intermediate (IV) is prepared by alkylation of 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinoline (V) with 4-(trifluoromethyl)benzyl bromide (VI) in the presence of LDA (generated in situ from butyl lithium and diisopropylamine) in THF/hexane. Enantioselective transfer hydrogenation of (IV) using triethylammonium formate and $Et_3N$ in the presence of dichloro(*p*-cymene)ruthenium dimer and (*R,R*)-mesitylenesulfonyl-1,2-diphenylethanediamine (MstDPEN) furnishes the tetrahydroisoquinoline derivative (VII), which can be converted to almorexant by three alternative routes. a) Alkylation with methyl α-bromophenylacetate (VIII) in the presence of DIEA in refluxing THF/dioxane/toluene providing amino ester (IX) as a diastereomeric mixture, which is further hydrolyzed with NaOH in aqueous methanol at 60 °C to yield carboxylic acid (X). Finally, compound (X) is condensed with methylamine hydrochloride in the presence of EDC and HOBt in DMF followed by chromatographic separation of the diastereomers. Alternatively, almorexant is obtained by alkylation of tetrahydroisoquinoline (VII) with either: b) α-bromo-*N*-methylphenylacetamide (XI) or c) 2(*S*)-tosyloxy-*N*-methylphenylacetamide (XII) by means of DIEA in hot THF or butanone (1). Scheme 1.

The bromo amide intermediate (XI) is prepared by condensation of phenylacetyl chloride (XIII) with *N*-methylhydroxylamine hydrochloride in the presence of $Et_3N$ in $CH_2Cl_2$ to produce the Weinreb amide (XIV), which is then acylated with methanesulfonyl chloride and $Et_3N$ followed by ultrasound-promoted rearrangement of the *N*-sulfonyloxy amide intermediate in the presence of DIEA and LiBr in acetonitrile (1). Scheme 2.

The chiral intermediate (XII) is obtained by aminolysis of methyl (*S*)-(+)-mandelate (XV) with methylamine in MeOH to give 2(*S*)-hydroxy-*N*-methylphenylacetamide (XVI), which is treated with *p*-toluenesulfonyl chloride in the presence of DMAP and DIEA in $CH_2Cl_2$ (1). Scheme 3.

**BACKGROUND**

Insomnia is a highly prevalent condition that may affect up to 10-15% of the population (2). To date, the mainstay of treatment has involved

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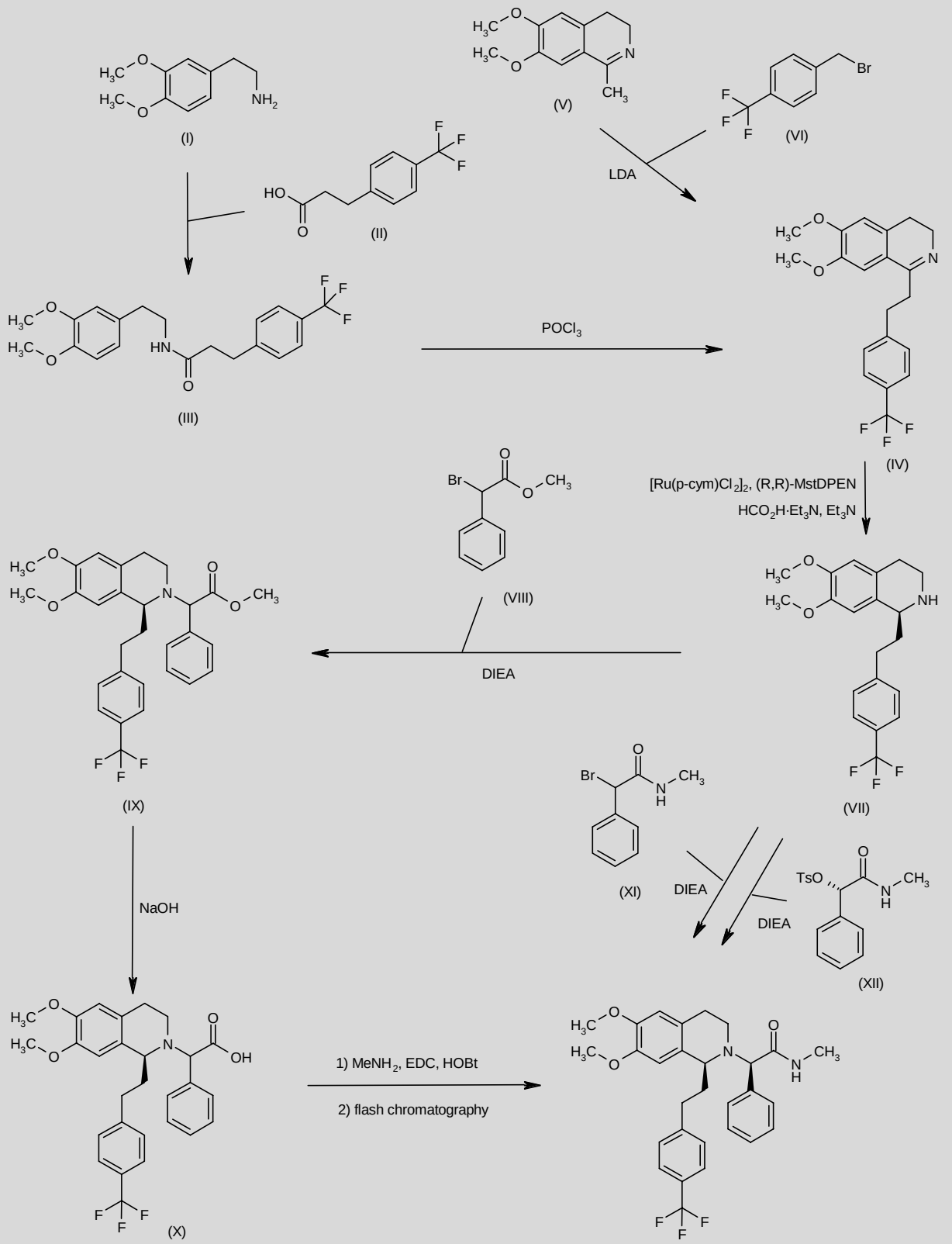
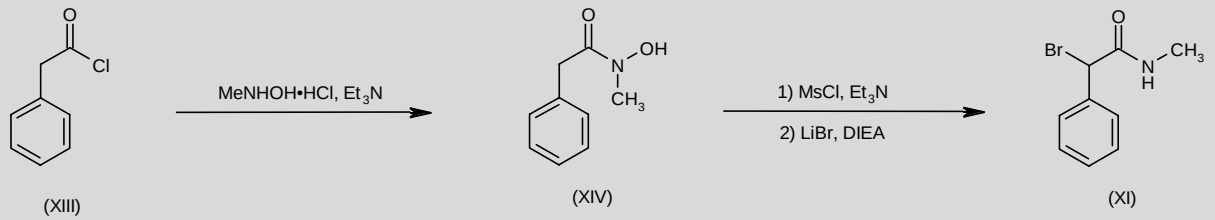
**Scheme 1.** Synthesis of Almorexant

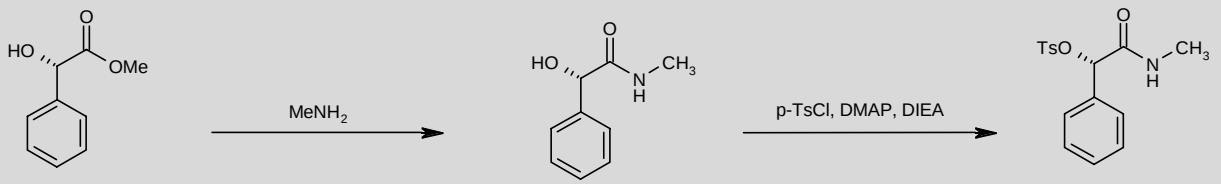


**Scheme 2.** Synthesis of Intermediate (XI)




(XIII) (XIV) (XI)

**Scheme 3.** Synthesis of Intermediate (XII)




(XV) (XVI) (XII)

GABAergic modulation via the benzodiazepines or the Z-drugs zolpidem, zopiclone, zaleplon and eszopiclone (3). More recently, melatonergic modulation via ramelteon, an $MT_1$ and $MT_2$ receptor agonist, has been introduced into clinical practice (4). Another sleep pathway is now being explored by manipulation of the orexin system. Orexins (also known as hypocretins) are excitatory neuropeptides produced by neurons in the lateral and posterior hypothalamus which send projections throughout the brain (5, 6). Orexins are ligands for two G protein-coupled receptors, $OX_1$ and $OX_2$. $OX_1$ receptors have been implicated in the modulation of rapid eye movement (REM) sleep (7), whereas a deficiency in $OX_2$ receptors may be involved in cataplexy and behavioral arrest (8). A dual $OX_1/OX_2$ receptor antagonist, almorexant (ACT-078573), was recently developed in an attempt to modify cerebral orexinergic tone and thus promote sleep.

## PRECLINICAL PHARMACOLOGY

Almorexant has demonstrated potent and highly selective affinity for the $OX_1$ and $OX_2$ receptors, with $IC_{50}$ values for the human $OX_1$ and $OX_2$ receptors of 13 and 8 nM, respectively. It had little or no affinity for a wide range of other receptors or enzymes even at concentrations of 10 μM (9).

When almorexant was administered orally at 10-100 mg/kg to male Wistar rats, there was a dose-dependent reduction in nocturnal home cage activity and time spent in the "active wake" period. These effects were statistically significant at doses of 30-300 mg/kg. Similar reductions were seen with zolpidem (100 mg/kg p.o.). Both zolpidem and almorexant increased non-REM (NREM) sleep, but whereas almorexant increased REM sleep in physiological proportion to NREM sleep, zolpidem decreased it (10). With chronic administration of 100 mg/kg p.o. almorexant for 5 days, there was no tolerance to the increased NREM sleep or decreased home cage activity compared with acute administration and no rebound on the discontinuation night. This was in contrast to zolpidem, which did show tolerance to increased NREM activity (11).

Body temperature was not affected by any dose of almorexant over a 12-h period, while zolpidem (100 mg/kg) induced a marked hypothermia. The sleep-promoting effects of 100 mg/kg almorexant could be quickly reversed by sensorimotor stimulation on the rotarod and grip tests, whereas zolpidem had detrimental effects at doses above 30 mg/kg (10).

In male beagle dogs, single oral doses of almorexant (10-100 mg/kg) dose-dependently decreased mobility scores compared to vehicle. Significant changes in relative times spent in quiet wake states and sleep postures were seen at 100 mg/kg. An increased incidence of distal muscle movements (e.g., of nose, lips, whiskers) was seen after 100 mg/kg, indirectly indicating increased REM sleep. As in rats, the effects of almorexant were immediately reversed when a familiar person entered the room, and sleep was resumed within 10 min of their departure. No cardiovascular or body temperature changes were noted (12). No episodes of muscular weakness were seen in rats at doses up to 300 mg/kg/day p.o. or in dogs at doses up to 125 mg/kg/day p.o. for up to 4 weeks, and no withdrawal signs on discontinuation (9).

The question arises as to whether $OX_1$ or $OX_2$ receptor blockade is key for sleep promotion. Some indirect evidence for a role for $OX_2$

blockade was provided by Dugovic et al. (13). The selective $OX_1$ antagonists SB-334867 and SB-408124 failed to demonstrate any sleep-promoting effects in rats at 30 mg/kg s.c. However, JNJ-10397409, an $OX_2$ antagonist, induced sleep promotion at doses of 3 µg/kg s.c. and 100 mg/kg p.o. The study also confirmed the sleep-promoting effects of almorexant at 100 mg/kg p.o.

## PHARMACOKINETICS AND METABOLISM

Almorexant rapidly crosses the blood–brain barrier in rats and reaches levels of approximately 2 µM (approx. 1000 ng/g) in the brain and approximately 6 µM in plasma 3 h after a dose of 100 mg/kg p.o. Almorexant is 99% bound to plasma proteins and thus brain concentrations are estimated to be 20 and 60 nM, respectively, at 3 and 6 h after 300 mg/kg p.o. Systemic bioavailability ranged from 8 to 34% in rats depending on formulation, dose or fasted or fed state. In dogs, the median time to peak plasma concentrations ($t_{max}$) ranged from 0.5 to 2 h, mean systemic bioavailability was 18-49% and elimination half-life ($t_{1/2}$) was 8-9 h. In rats and dogs treated with 100-300 mg/kg and 25-125 mg/kg p.o., respectively, for 28 days there was no evidence of drug accumulation despite high systemic exposure (9).

In a randomized, double-blind, placebo- and active-controlled, single-ascending-dose study in 70 male subjects (18-37 years), median $t_{max}$ values ranged from 0.7 to 2.3 h after doses of 5-1000 mg almorexant. After attainment of peak plasma concentrations ($C_{max}$), almorexant levels declined rapidly by about 80% at 8 h after $t_{max}$. The distribution half-life was about 1.4 h and the elimination $t_{1/2}$ ranged from 13 to 19 h at doses of 200-1000 mg. An accurate elimination $t_{1/2}$ could not be determined at doses below 200 mg due to assay sensitivity limitations. Exposure to almorexant was approximately dose-proportional based on area under the curve (AUC) values (14).

In a prospective, single-center, randomized, double-blind, placebo-controlled, multiple-ascending-dose study in healthy male and female subjects, almorexant 100, 200, 400 or 1000 mg was administered for up to 6 days. Almorexant was administered in the morning on days 1-4 and in the evening on days 5-6. Following multiple-dose administration in the mornings, almorexant was rapidly absorbed ($t_{max}$ = 1-1.5 h), with marked distribution after attainment of $C_{max}$. The terminal elimination $t_{1/2}$ ranged from 18.9 to 23.8 h after doses of 100-1000 mg on days 1-4. With evening administration, $t_{max}$ values ranged from 2 to 4 h and elimination $t_{1/2}$ from 15.0 to 22.2 h. No major differences between genders were seen in the pharmacokinetic profile. No relevant accumulation was observed with repeated dosing up to 6 days; the accumulation index was 1.1-1.5 (15).

## SAFETY

During toxicological and toxicokinetic studies, rats and dogs were dosed for 13 weeks with up to 200 mg/kg/day and up to 40 mg/kg/day, respectively. In none of these studies was a drug-related abrupt loss of muscle tone or cataplexy reported in either species (9).

A randomized, double-blind, placebo- and active-controlled, single-ascending-dose study in 70 healthy male subjects assessed the safety and tolerability of single doses of 1-1000 mg almorexant (n = 6/dose group), 10 mg zolpidem (n = 14) and placebo (n = 14). Most adverse events were mild and no serious adverse events were reported. No significant effects on blood pressure or ECG were noted in any group and no changes in 11 different plasma hormones (growth hormone, luteinizing hormone-releasing hormone, corticotropin-releasing factor, adrenocorticotropic hormone, thyroid-stimulating hormone, prolactin, testosterone, cortisol, orexin-A, leptin and ghrelin) over 24 h in the 400- and 1000-mg almorexant dose groups. Almorexant at doses above 200 mg and zolpidem elicited reports of somnolence, dizziness, diplopia, attention disturbances and fatigue, in contrast to no reports with placebo. However, zolpidem was also associated with reports of abnormal coordination (4 reports) and feeling drunk (2 reports), whereas almorexant was not. The most commonly reported adverse event for almorexant was somnolence (n = 4 at 200 and 400 mg; n = 5 at 1000 mg); there were 5 reports with zolpidem in 14 subjects (14).

A prospective, single-center, double-blind, randomized, placebo-controlled, ascending-dose study in 44 male and female subjects assessed the safety and tolerability of almorexant at doses of 100 (n = 9), 200 (n = 8), 400 (n = 9) and 1000 mg (n = 9) and placebo (n = 9) for 6 days. Almorexant was administered in the morning for 4 days and in the evening for 2 days. The most common adverse events were somnolence and fatigue. The incidence of these events in the placebo group was 44.4% (4 of 9 patients), and the incidence of somnolence with almorexant was 44.4%, 87.5%, 100% and 100%, respectively, in the 100-, 200-, 400- and 1000-mg groups. Fatigue was reported in 22.2%, 25.0%, 33.3% and 44.4%, respectively. There were no clinically relevant changes in vital signs, ECG or laboratory parameters in any group (15).

A multicenter, randomized, double-blind, placebo-controlled, single-dose, crossover study assessed the safety and efficacy of almorexant 50, 100, 200 and 400 mg given at night in 147 patients with primary insomnia (16). The incidence and intensity of adverse events increased with dose. The only serious adverse event was vasovagal syncope in a placebo recipient. Fatigue (n = 5) and dry mouth (n = 4) were the most common adverse events in the 400-mg almorexant group; the corresponding values in the placebo group were 1 and 0 reports, respectively.

## CLINICAL STUDIES

A randomized, double-blind, placebo- and active-controlled study assessed the pharmacodynamic and sleep-promoting effects of almorexant 1-1000 mg (n = 42), zolpidem 10 mg (n = 14) and placebo (n = 14) in healthy male subjects. Almorexant (400 and 1000 mg) and zolpidem decreased adaptive tracking, saccadic peak velocity and subjective alertness, and increased body sway compared to placebo. These effects were apparent within approximately 1 h postdose, peaked at 2 h and had a duration of approximately 6-8 h (17). Doses of almorexant above 200 mg significantly and dose-dependently decreased latency to stage 2 sleep; zolpidem caused a numerical but not a statistical reduction in stage 2 sleep versus placebo. These effects disappeared 6.5 h postdose except in the 1000-mg group. There were no relevant effects on immediate–delayed memory recall with placebo or active drugs. Repeated doses of almorexant (100-1000 mg) over 4 days did not result in more pronounced effects on saccadic peak velocity, adaptive track-

***Table I.*** *Effects of almorexant on selected sleep variables in patients with primary insomnia (data from Ref. 16).*

| | | | Mean values (in % for SE and min for LPS and WASO) | | |
|---|---|---|---|---|---|
| Sleep parameter/Dose | N | Mean treatment effect | Placebo | Almorexant | *P* value |
| *Sleep efficiency* | | | | | |
| 400 mg | 39 | 14.4 | 71.0 | 85.4 | < 0.001 |
| 200 mg | 38 | 8.2 | 75.6 | 83.8 | < 0.001 |
| 100 mg | 38 | 4.6 | 78.1 | 82.7 | 0.019 |
| 50 mg | 32 | 3.3 | 75.4 | 78.7 | NS |
| *Latency to persistent sleep* | | | | | |
| 400 mg | 39 | –18.0 | 54.2 | 36.2 | < 0.05 |
| 200 mg | 38 | –10.4 | 38.7 | 28.2 | not stated |
| 100 mg | 38 | –10.4 | 46.9 | 36.5 | not stated |
| 50 mg | 31 | –5.7 | 49.6 | 43.9 | not stated |
| *Wake after sleep onset* | | | | | |
| 400 mg | 39 | –54 | 94.0 | 40.0 | < 0.0001 |
| 200 mg | 38 | –34.3 | 86.9 | 52.7 | not stated |
| 100 mg | 38 | –20.1 | 68.5 | 48.4 | not stated |
| 50 mg | 32 | –6.7 | 69.6 | 62.0 | not stated |

NS, not significant.

ing or subjective alertness when the day 4 and day 1 results were compared. There were no detrimental effects on word recall in any group (15).

A randomized, double-blind, placebo-controlled, single-dose, 2-way crossover study in 147 patients with primary insomnia demonstrated the efficacy of 400 mg almorexant on sleep efficiency, the primary endpoint. Thereafter, the minimal effective dose to decrease sleep efficiency was determined. Secondary endpoints included latency to persistent sleep (LPS) and wake after sleep onset (WASO) duration. The key results are summarized in Table I. Next-day performance on fine motor test and reaction time were also measured. Almorexant significantly increased sleep efficiency at doses as low as 100 mg and dose-related decreases in LPS and WASO were also seen versus placebo. There were no significant effects on motor function or reaction time the following day (16).

A multicenter, double-blind, randomized, placebo-controlled, 5-period/5-way crossover study in elderly (65+ years) patients with primary insomnia assessing the safety and efficacy of almorexant 25-200 mg has been completed (18), and a phase III study in adults with chronic primary insomnia (RESTORA 1, REstore physiological Sleep with The Orexin Receptor antagonist Almorexant) is recruiting approximately 670 patients in 70 centers around the world to confirm the effects on sleep induction and maintenance, including an active reference arm with zolpidem (19).

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Actelion Pharmaceuticals, Ltd. (CH); being developed in collaboration with GlaxoSmithKline.

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