

Programa Cooperación Farma-Biotech
8º encuentro (7 de mayo de 2013)

Lorediplon: “best-in-class” product for insomnia treatment



Madrid, 7 de mayo de 2013

Programa Cooperación Farma-Biotech

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The Company

Who we are

International privately-held pharmaceutical company

Founded in 1959

Business areas

Pharmaceuticals

OTCs & personal health

Diagnostics

Fine chemicals

Food & feed additives

Mission

To advance the wellbeing of society

Worldwide operations

Headquarter in Barcelona

Presence in 93 countries

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The Company

Total turnover 2012	€819 million (+2% vs 2011)
International turnover	€365 million (44% of total)
Total staff 2012	2,201 (abroad 593)
Investment in R&D	12.1% of prescription sales

**Given the maximum rating by the Spanish national
pharma assessment system (Profarma)**

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The Product - Target Indication

Insomnia

In **2010**, there were **53 million** prevalent cases of insomnia in the **7 MM** (US, Japan, France, Germany, Italy, Spain, and UK).

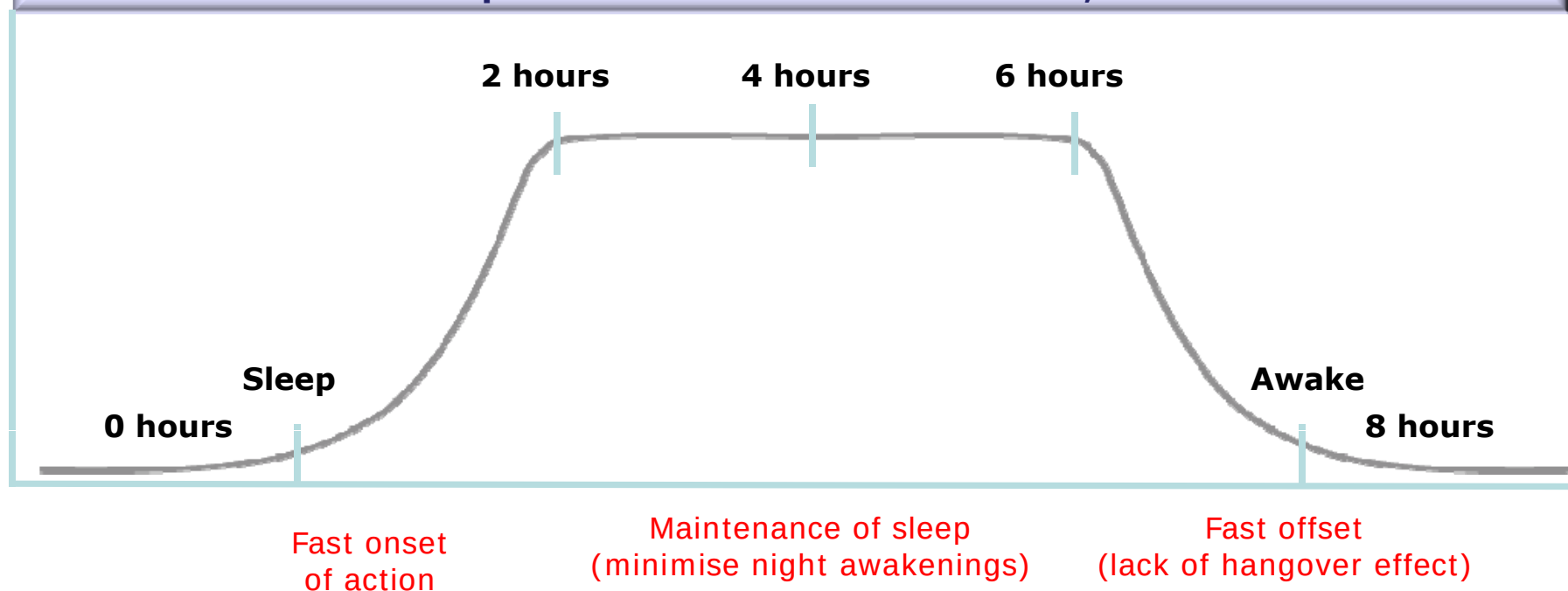
US (25.7 million), Japan (8.2 million), France (6.8 million), Germany and Italy (3.5 million), Spain and the UK (2.5 million).

Datamonitor estimates that by **2020**, nearly **56 million** adults over 18 years will be living with insomnia in these markets

Insomnia Therapeutic Global Market was about **2.8 b\$** in **2010**

Insomnia – Unmet Clinical Needs

- ❑ 50% insomnia patients underserved
- ❑ 39 millions 7MM suffer sleep maintenance
- ❑ Residual effects of zolpidem, eszopiclone and suvorexant compounds
- ❑ Gold standard Zolpidem
- ❑ Balance between sleep maintenance & residual effects, the unmet clinical need



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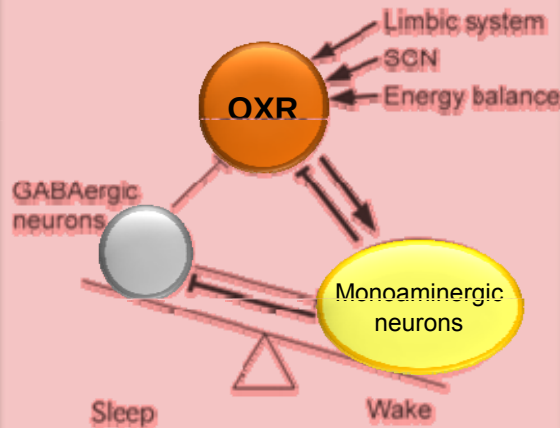
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The Product - Mechanisms of action

Tendency to sleep is determined by balance of opposing neurotransmitters

Awake promoting system:

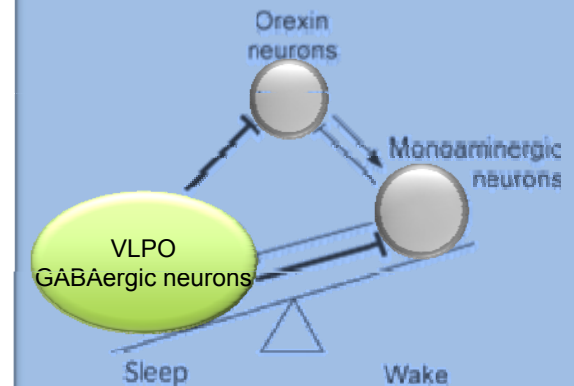
Orexin
Histamine
Norepinephrine
Serotonin
AcetylCholine



Product	$\alpha 1$ GABA _A affinity (ki nM)
Lore diplon	2.1
Zaleplon	182.6
Eszopiclone	50.1
Zolpidem	38.2

Sleep promoting system:

GABA
Galanin
Adenosine
Melatonin



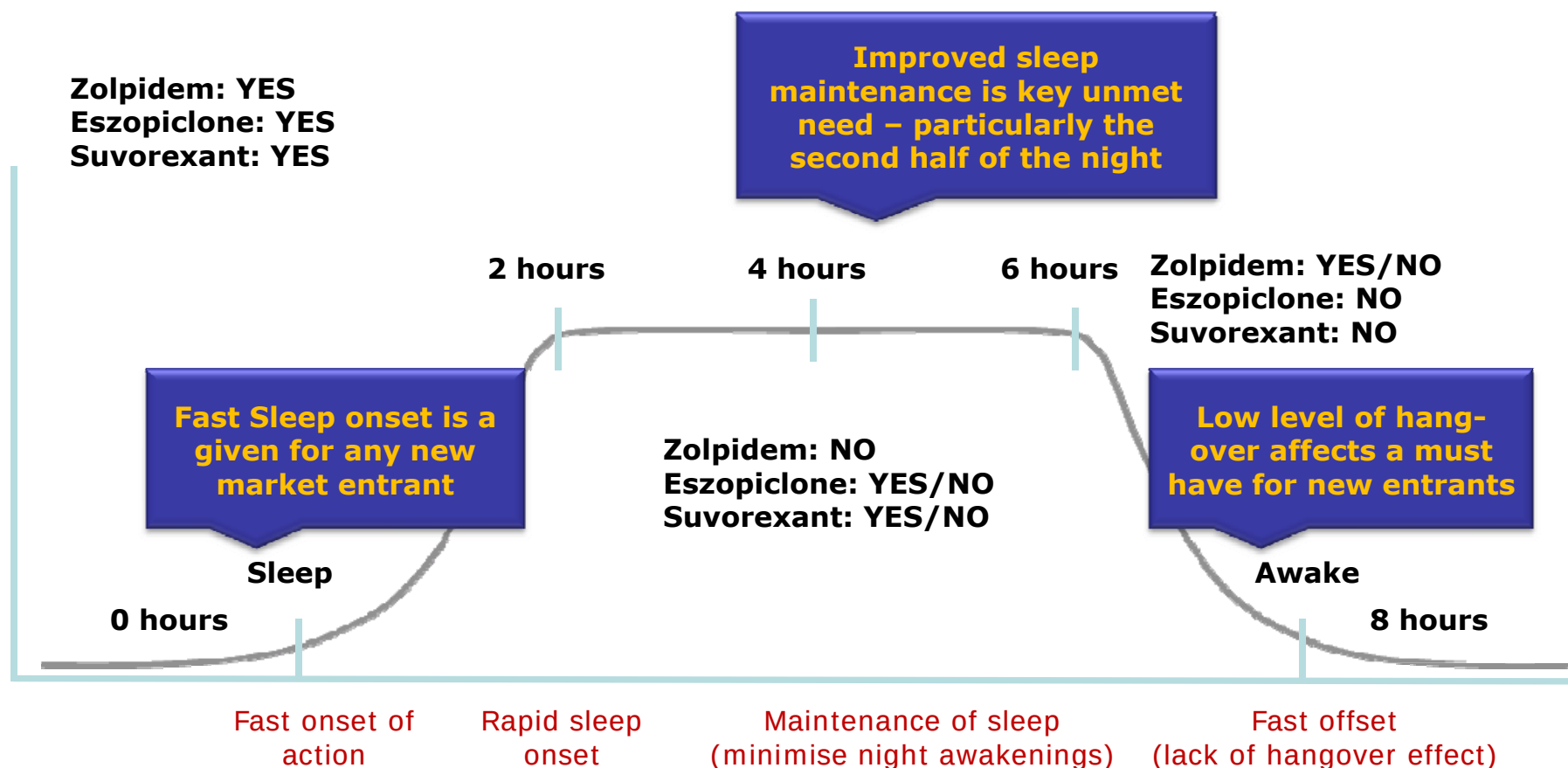
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The Product - Differential features facing the market

Competitor	Status	Mechanism of action
MARKETED COMPOUNDS		
Ambien, Zolpidem tartrate	Marketed	GABAergic
Ambien CR, Zolpidem tartrate	Marketed	GABAergic
Lunesta, Eszopiclone	Marketed	GABAergic
Zolpidem Sublingual /spray form. (Edluar, Intermezzo, Zolpimist...)	Marketed	GABAergic
Sonata, Zaleplon	Marketed	GABAergic
Ramelteon, Rozerem	Marketed	Melatonin agonist
Circadin, Prolonged-release melatonin	Marketed	Melatonin agonist
Doxepin, Silenor	Marketed	Histamine H1 antagonists
<i>Xanax, Klonopin, Valium, Ativan, etc</i>	Marketed	Benzodiazepines
COMPOUNDS IN DEVELOPMENT		
Suvorexant (Merck)	NDA	Orexin antagonist
Tasimelteon (Vanda)	Phase III (2010)	Melatonin agonist
Filorexant (Merck)	Phase II (2012)	Orexin antagonist
SB-649868 (GSK)	Phase II (2006)	Orexin antagonist
ITI-722 (Intracellular Therapies)	Phase II (2007)	5HT2A anta/dopamine modul.
Pimavanserin tartrate (Acadia)	Phase II (2003)	5HT2A inverse agonist
Piromelatine (Neurin)	Phase II (2011)	Melatonin agonist
INT-0020 (IntelGenx)	Phase II (2012)	Unknown
Zaleplon, additional formulations	Phase II (2012/13)	GABAergic
E-2006 (Eisai)	Phase I (2011)	Unknown

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The Product - Differential features facing the market



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The Product - Differential features facing the market

Target Product Profile

Indication	Insomnia
Mechanism of Action	Modulation of GABA _A receptor
Dosing regimen	<i>Once a night</i> oral tablet
Duration of treatment	Short term & chronic
Efficacy	Better . Sleep maintenance . Sleep quality
Safety	Similar/better than zolpidem/eszopiclone & Suvorexant . Next day hangover effects

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The Product - Differential features facing the market

Key Opinion Leaders Inputs

Lorediplon vs Z-drugs:

- Ambien is, from a commercial and clinical point of view, the gold standard
- **50% of Ambien patients continue suffering sleep maintenance problem**
- **FDA requirement to reduce Ambien dose** represents an opportunity if we are able to demonstrate better next day profile
- Better sleep maintenance than Ambien will give a 200 – 300 M market share in US

Lorediplon vs Orexin antagonists:

- Orexin antagonists are supposed to have a **better safety profile** in terms of:
 - amnesia
 - dependence and abuse
 - rebound insomnia
 - respiratory depression
- But Orexin antagonists **are not expected to replace completely z drugs** and
- **Suvorexant** is showing **next day hangover effects**.

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The Product - Differential features facing the market

Insomnia Patient Opportunity Algorithm - USA

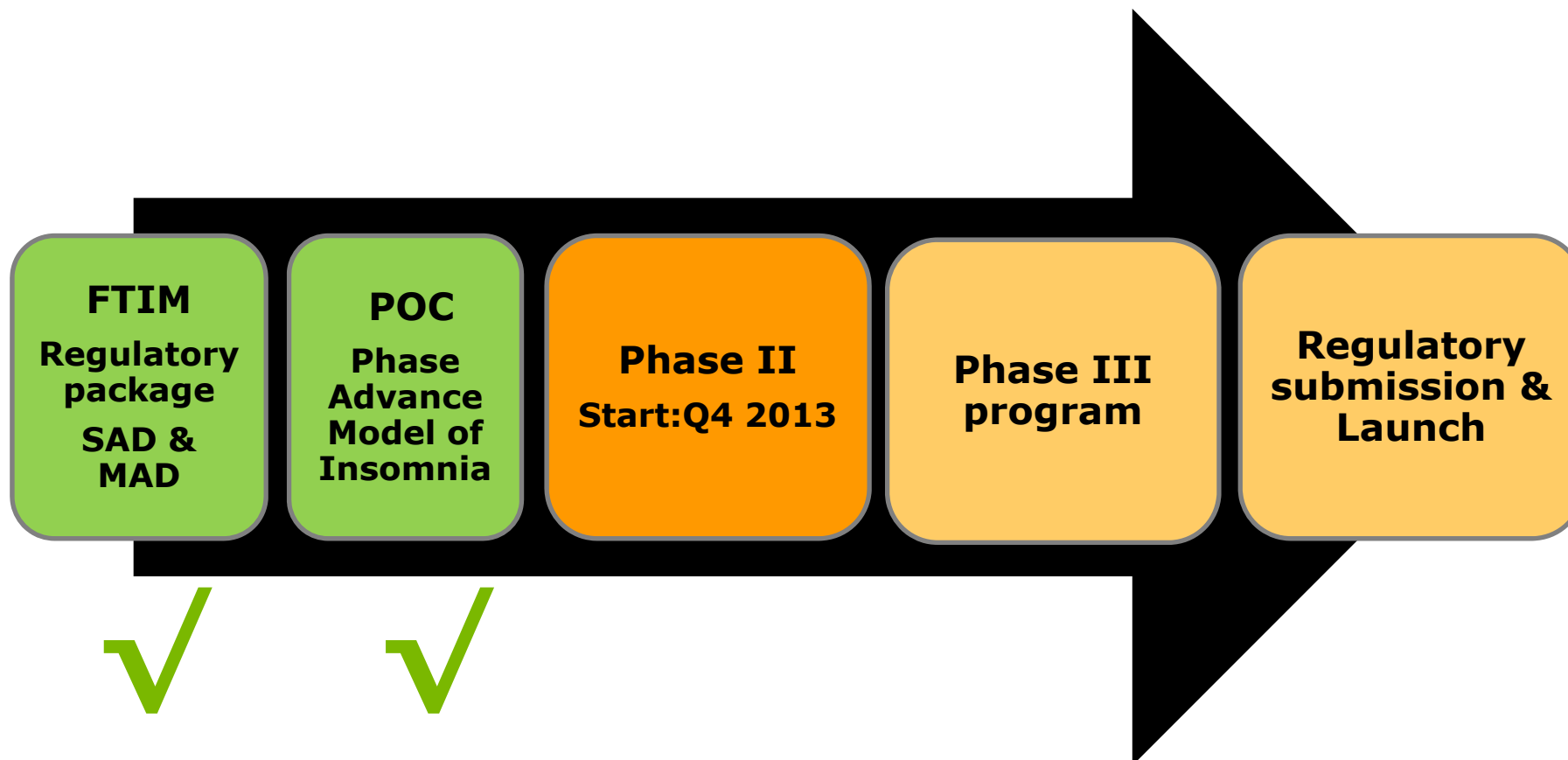
	Patient Pool ('000s)
US population	314,000
% suffer insomnia	10%
% diagnosed	56%
% drug treated	70%
Total treated	12,309
Number of patients underserved	6,154



'000s (US\$, M)		
Peak share underserved	Suvorexant Patients	Lore diplon Patients
Suvorexant Launch	4,308 (840M)	
Lore diplon launched	3,754 (730M)	1,416 (280M)

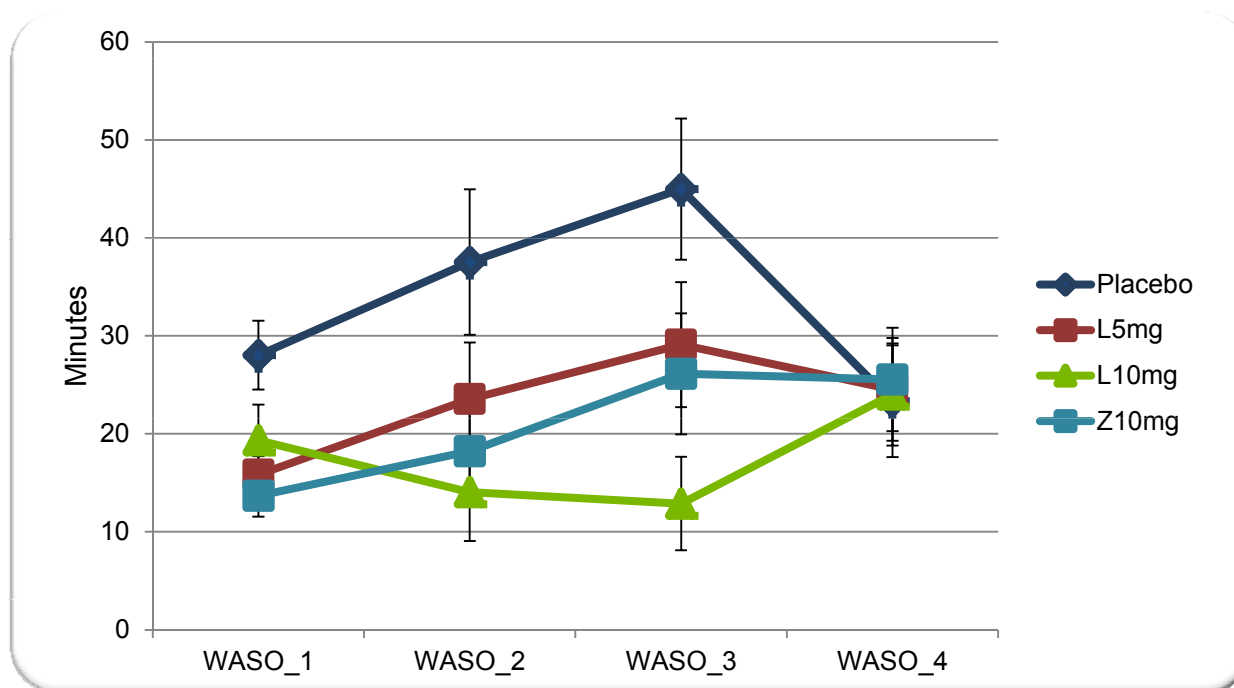


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The Product - Current status of development



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The Product - Current status of development

Lorediplon targets Sleep Maintenance



- **Lorediplon 10 mg** progressively **reduced WASO** over the first 3 quarters of the **night** (hours 1-6), importantly returning to baseline in the fourth quarter therefore with no negative effects on morning functioning.
- **Zolpidem 10 mg** had a main **WASO** effect on the first two quarters of the **night** and showed a reduced effect between 3-8 hours.

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The Product - Current status of development

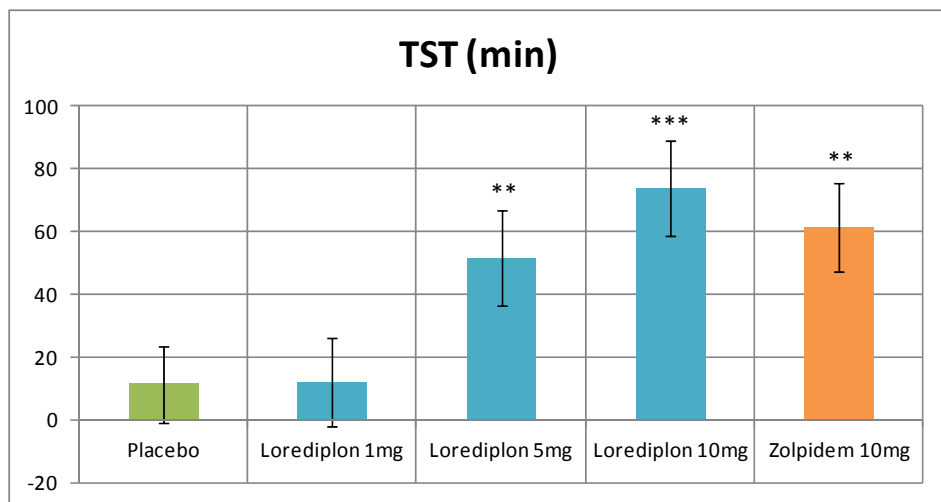
Lorediplon targets Sleep Maintenance

	Lorediplon 10mg*	Zolpidem IR 10mg*	Zolpidem IR 10mg**	Zolpidem CR 12.5 mg***	Eszopiclone 2mg****	Doxepin 6mg•
WASO Wake after sleep Onset	↓ 79 mins	↓ 60 mins	↓ 40 mins	↓ 33.5 mins	↓ 36 mins	↓ 29 mins

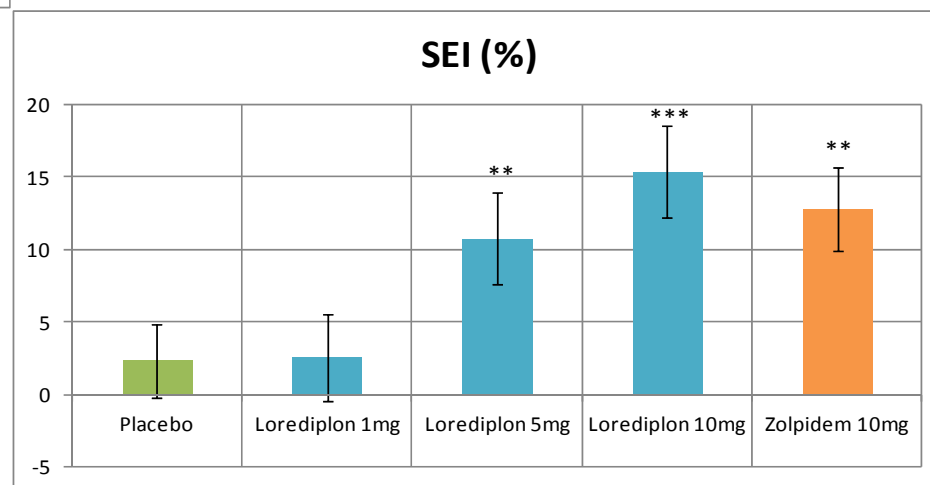
*Internal study Phase Advance, ** Phase advance, Sleep 30 (5) 2007,
Phase III, Sleep 31 (1) 2008, * Phase IV patients, Sleep 33 (2),
•Krystal AD 2011

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The Product - Current status of development

Lorediplon targets Sleep Maintenance

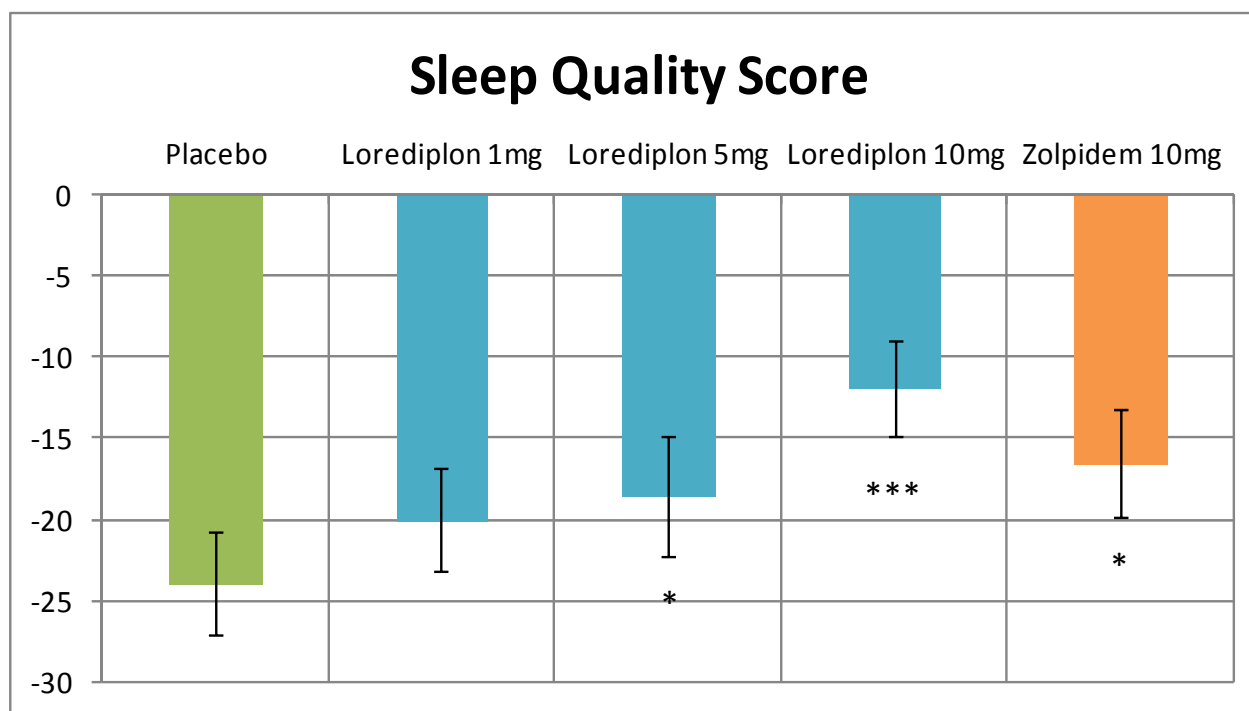


** $p \leq 0.01$ vs placebo
*** $p \leq 0.001$ vs placebo
TST = Total Sleep Time
SEI = Sleep Efficiency Index



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The Product - Current status of development

Lorediplon targets sleep Quality



* $p < 0.05$ vs placebo; *** $p \leq 0.001$ vs placebo

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The Product - Current status of development

Lorediplon does not show next day hangover effects

Parameter	Lorediplon 1mg	Lorediplon 5mg	Lorediplon 10mg	Zolpidem 10mg
Sleep Visual Analogue scale				
Awakening easiness	ns	ns	ns	ns
Awakening behaviour	ns	ns	ns	ns
Psychomotor Vigilance Test (attention)				
Mean reaction time	ns	ns	ns	ns
Minimum reaction time	ns	ns	ns	ns
Number of lapses	ns	ns	ns	ns
Maximun reaction time	ns	ns	ns	ns
Digit Span Test (memory)				
Total score	ns	ns	ns	ns

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The Product - IPR protection

PATENT TYPE	FILED	APPROVAL DATES	
Composition of matter	June 2005	Australia EP China Hong Kong Japan Mexico Peru Philippines Russia Taiwan USA	Dec 2011 May 2010 July 2011 Sep 2010 May 2012 Sep 2010 April 2008 June 2011 January 2013 Sept. 2012 In process
Polymorph B	October 2006	China Japan Mexico US	March 2012 January 2013 December 2011 October 2011
Amorphous Form	November 2007	EP China Mexico Russia USA	January 2013 Nov. 2012 February 2012 May 2012 December 2012
Industrial Process	January 2009	Mexico US	August 2012 April 2012
Synthetic process	October 2006	Australia EP Chile China Hong Kong Mexico Russia US	October 2012 March 2011 August 2011 June 2012 June 2011 July 2011 Nov 2010 August 2011

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The Product - Pitfalls & Risks to be considered

Technical

- **Next day hangover effects**

Commercial

- **Price in Europe**

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Partnering Opportunities

Unmet need

Balance **sleep maintenance** and residual effects

Value proposition

Best in class GABA agonist addressing insomnia unmet need
Estimated Market share in US 280M

Partnering proposal

Partners/licensees for the further development (Phase II and beyond) and **commercialization** on either a world-wide or territory basis

Value of Asset (rNPV)

@ Phase II ready		Margin		
		15%	25%	35%
Peak Market Share	10%	(0.2)	8	17
	20%	13	30	47
	30%	25	51	77

@ Phase III ready		Margin		
		15%	25%	35%
Peak Market Share	10%	6	27	48
	20%	37	79	122
	30%	69	132	195