



## Clinical trial results:

### A Phase III Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of Suvorexant (MK-4305) for the Treatment of Insomnia in Subjects with Alzheimer's Disease

#### Summary

EudraCT number	2015-003154-40
Trial protocol	FI GB IT
Global end of trial date	30 September 2018

#### Results information

Result version number	v1 (current)
This version publication date	13 October 2019
First version publication date	13 October 2019

#### Trial information

##### Trial identification

Sponsor protocol code	MK-4305-061
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02750306
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2018
Global end of trial reached?	Yes
Global end of trial date	30 September 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This study's main objective was to examine the safety and efficacy of suvorexant (MK-4305) to improve sleep in individuals with Alzheimer's disease (AD). The primary hypothesis for the study was that suvorexant is superior to placebo in improving insomnia as measured by change from baseline in polysomnography (PSG)-derived total sleep time (TST) at Week 4.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Peru: 68
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 187
Worldwide total number of subjects	285
EEA total number of subjects	27

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	83
From 65 to 84 years	193
85 years and over	9

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study included participants who had a diagnosis of probable Alzheimer's disease and had sleep complaints that met DSM-5 criteria for a diagnosis of insomnia.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Suvorexant

Arm description:

Participants received 1 suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' suvorexant dose could be increased to 20 mg if their Clinical Global Impression of Insomnia Severity (CGI-S) was >3 and investigators felt they could tolerate the increased dose.

Arm type	Experimental
Investigational medicinal product name	Suvorexant
Investigational medicinal product code	
Other name	MK-4305
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 1 suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' suvorexant dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.

<b>Arm title</b>	Placebo
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Arm description:

Participants received 1 placebo-matching suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' placebo-matching dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants receive 1 placebo-matching suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' placebo-matching dose can be increased to 20 mg if their CGI-S is >3 and investigators feel they can tolerate the increased dose.

<b>Number of subjects in period 1</b>	Suvorexant	Placebo
Started	142	143
Completed	136	141
Not completed	6	2
Consent withdrawn by subject	5	2
Protocol deviation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Suvorexant
Reporting group description:	
Participants received 1 suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' suvorexant dose could be increased to 20 mg if their Clinical Global Impression of Insomnia Severity (CGI-S) was >3 and investigators felt they could tolerate the increased dose.	
Reporting group title	Placebo
Reporting group description:	
Participants received 1 placebo-matching suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' placebo-matching dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.	

Reporting group values	Suvorexant	Placebo	Total
Number of subjects	142	143	285
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	69.6	69.1	-
standard deviation	± 8.7	± 8.5	-
Sex: Female, Male Units: Subjects			
Female	91	95	186
Male	51	48	99
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	12	17
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	24	22	46
White	86	80	166
More than one race	25	25	50
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	89	93	182
Not Hispanic or Latino	52	50	102
Unknown or Not Reported	1	0	1
Polysomnography-derived Total Sleep Time			
Note: One participant who failed the screening was inadvertently randomized and treated with suvorexant; had no polysomnography-derived total sleep time data.			
Units: Minutes			
arithmetic mean	279.1	271.2	-
standard deviation	± 76.6	± 86.7	-



## End points

### End points reporting groups

Reporting group title	Suvorexant
Reporting group description: Participants received 1 suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' suvorexant dose could be increased to 20 mg if their Clinical Global Impression of Insomnia Severity (CGI-S) was >3 and investigators felt they could tolerate the increased dose.	
Reporting group title	Placebo
Reporting group description: Participants received 1 placebo-matching suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' placebo-matching dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.	

### Primary: Change from Baseline in Polysomnography-derived Total Sleep Time (TST) at Week 4

End point title	Change from Baseline in Polysomnography-derived Total Sleep Time (TST) at Week 4
End point description: TST was measured at Baseline and at Week 4 in a sleep laboratory by polysomnography, during an 8-hour recording period beginning at participants' habitual bedtime. The analysis population for this end point included all randomized participants who received at least 1 dose of study medication, had a baseline value for change from baseline analyses, and at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of study medication.	
End point type	Primary
End point timeframe: Baseline and Week 4	

End point values	Suvorexant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	139		
Units: Minutes				
least squares mean (confidence interval 95%)	73.4 (61.3 to 85.5)	45.2 (33.3 to 57.2)		

### Statistical analyses

Statistical analysis title	Change from Baseline in TST at Week 4
Comparison groups	Suvorexant v Placebo



Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00128 <sup>[1]</sup>
Method	ANCOVA
Parameter estimate	Difference in Least Squares Means
Point estimate	28.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	45.2

Notes:

[1] - P-Value for the Difference in Least Squares Means

### Primary: Percentage of Participants Who Experienced One or More Adverse Events

End point title	Percentage of Participants Who Experienced One or More Adverse Events <sup>[2]</sup>
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End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The analysis population for this end point included all randomized participants who received at least 1 dose of study medication.

End point type	Primary
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End point timeframe:

Up to 6 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No between-group statistical analysis was performed for this end point.

End point values	Suvorexant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	143		
Units: Percentage of participants				
number (not applicable)	22.5	16.1		

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event <sup>[3]</sup>
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End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The

analysis population for this end point included all randomized participants who received at least 1 dose of study medication.

End point type	Primary
End point timeframe:	
Up to 4 weeks	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No between-group statistical analysis was performed for this end point.

<b>End point values</b>	Suvorexant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	143		
Units: Percentage of participants				
number (not applicable)	0.7	0.7		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Polysomnography-derived Wakefulness After Persistent Sleep Onset (WASO) at Week 4

End point title	Change from Baseline in Polysomnography-derived Wakefulness After Persistent Sleep Onset (WASO) at Week 4
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End point description:

WASO was measured at Baseline and at Week 4 in a sleep laboratory by polysomnography during an 8-hour recording period beginning at participants' habitual bedtime. The analysis population for this end point included all randomized participants who received at least 1 dose of study medication, had a baseline value for change from baseline analyses, and at least 1 post-randomization observation for the analysis endpoint subsequent to at least 1 dose of study medication.

End point type	Secondary
End point timeframe:	
Baseline and Week 4	

<b>End point values</b>	Suvorexant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Minutes				
least squares mean (confidence interval 95%)	-45.0 (-53.8 to -36.3)	-29.4 (-38.1 to -20.7)		

## Statistical analyses

<b>Statistical analysis title</b>	Change from Baseline in WASO at Week 4
Comparison groups	Suvorexant v Placebo

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01354 <sup>[4]</sup>
Method	ANCOVA
Parameter estimate	Difference in Least Squares Means
Point estimate	-15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.1
upper limit	-3.3

Notes:

[4] - P-Value for the Difference in Least Squares Means

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Up to 6 weeks

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study medication

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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### Reporting groups

Reporting group title	Suvorexant
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Reporting group description:

Participants received 1 suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' suvorexant dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.

Reporting group title	Placebo
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Reporting group description:

Participants received 1 placebo-matching suvorexant tablet every night for up to 4 weeks. After 2 weeks of double-blind treatment at 10 mg, participants' placebo-matching dose could be increased to 20 mg if their CGI-S was >3 and investigators felt they could tolerate the increased dose.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There were no non-serious adverse events that met the incidence greater than 5% threshold.

Serious adverse events	Suvorexant	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 142 (0.70%)	0 / 143 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Suvorexant	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 142 (0.00%)	0 / 143 (0.00%)	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2017	Amendment 1: The primary reason for this amendment was to incorporate changes to various sections of the protocol, including Trial Summary, Subject Inclusion Criteria, Subject Exclusion Criteria, Stratification, Concomitant Medications Allowed, and others.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported