

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Daridorexant for Insomnia

NIHRI ID	13281	NICE ID	10196
Developer/Company	Idorsia Pharmaceuticals Ltd	UKPS ID	Not available

Licensing and market availability plans	Currently in Phase III trials.
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*COMMERCIAL IN CONFIDENCE

SUMMARY

Daridorexant is a medicinal product in clinical development for the treatment of adults with insomnia. Insomnia means regularly having problems sleeping, which results in impaired daytime functioning. Insomnia can be categorised according to its duration, into short-term insomnia (lasting less than 4 weeks) and long-term (or persistent) insomnia (lasting 4 weeks or longer).

Daridorexant is a drug which reduces excessive alertness, in contrast to treatments of insomnia that sedates the central nervous system. As a result, daridorexant offers the potential to induce and maintain sleep, through all stages of sleep. Daridorexant is quickly absorbed in the body, resulting in a fast onset of action. Daridorexant is given orally as tablets. If licensed, daridorexant could represent an additional treatment option for patients with insomnia.

PROPOSED INDICATION

Adult and elderly patients with insomnia.^{1,2}

TECHNOLOGY

DESCRIPTION

Daridorexant (ACT-541468) is a dual orexin receptor antagonist (DORA). DORAs specifically target excessive alertness, in contrast to treatments of insomnia that act via broad sedation of the central nervous system. As a result, Daridorexant offers the potential to improve all stages of sleep and preserve the sleep architecture with a maintained efficacy in chronic insomnia patients.³

Daridorexant is in clinical development for the treatment of adult and elderly patients with insomnia. Two pivotal phase III confirmatory studies (NCT03545191, NCT03575104) are replicating primary outcome assessments at 1 and 3 months based on polysomnography data, whereas secondary endpoints include the overall self-reported night-time and day-time benefit using validated patient reported outcome instruments. An extension study is assessing the long-term safety and tolerability of daridorexant over a period of 40 additional weeks.⁴ Across phase III trials (NCT03545191, NCT03575104 and NCT03679884), 10mg, 25mg or 50mg daridorexant will be administered orally as tablets once daily in the evening.

INNOVATION AND/OR ADVANTAGES

Targeting the orexin receptor system for the treatment of insomnia offers an additional and alternative pharmacological approach to the more common gamma aminobutyric acid agonist sedative hypnotic treatments, the current pharmacological options for the treatment of insomnia, that insufficiently meet the needs of all insomnia patients.⁵

Currently in the UK there are no medicinal products of this class (DORA) and pharmacological mechanism of action licensed for the treatment of insomnia.⁶

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daridorexant is not currently licensed for any indication in the EU/UK.

PATIENT GROUP

DISEASE BACKGROUND

Insomnia is summarised as difficulty getting to sleep, difficulty staying asleep, early wakening, or non-restorative sleep despite adequate time and opportunity to sleep, resulting in impaired daytime functioning, such as poor concentration, mood disturbance, and daytime tiredness.⁷ Insomnia can be categorised according to duration or likely duration, including short-term insomnia (lasting less than 4 weeks) and long-term (or persistent) insomnia (lasting 4 weeks or longer).⁷

Insomnia may be associated with stress, psychiatric comorbidities, medical comorbidities, drug and substance misuse, or current medication (secondary insomnia).⁷ However, in up to 20% of people with persistent insomnia, there is no associated cause or comorbidity (primary insomnia).⁷ Patients with insomnia are less productive workers, show an increased risk for errors with higher frequency of motor vehicle and workplace accidents, and utilize medical health care systems to a greater degree than subjects with normal sleep pattern.⁸ Patients with insomnia can experience deterioration in their general health because of associated symptoms of daytime fatigue and decreased cognitive, social, and physical functioning.⁸ Insomnia also poses an economic burden as a result of increases in work-related accidents, higher work absenteeism, decreased job performance, and increased use of

health care resources.⁸ Insomnia has been implicated in higher risk of suicidal ideation and exacerbation of mood disorders and is also implicated in the pathogenesis of Alzheimer's disease.⁵ Chronic insomnia is associated with cardiovascular and cerebrovascular diseases, and increased mortality.^{9,10}

CLINICAL NEED AND BURDEN OF DISEASE

The reported prevalence rates of insomnia are highly variable and not many well conducted epidemiological studies are available. Population surveys indicate a 1-year prevalence of insomnia complaints of about 30-45% in adults.¹¹ The prevalence of primary insomnia, based the Diagnostic and Statistical manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria, has been estimated between 1 and 10% of the general adult population and up to 25% in the elderly.¹¹ In specialised centres for sleep disorders, approximately 80% of patients suffer from chronic insomnia; 15 to 25% of these individuals with chronic insomnia are diagnosed with primary insomnia.¹¹ In younger patients, insomnia with problems in sleep onset is more prevalent whereas in older patients sleep maintenance is more affected.¹¹ It is estimated that sleep-related productivity losses in the UK amount to £30bn annually.¹²

The Great British Sleep Survey (2011) identified that 5,083 participants (45.7%) out of 11,129 adults over 18 years of age who took the survey, were screened as having possible insomnia disorder.¹³ Using the GB population data from the same year, we can then conclude that 28,092,168 people approximately will experience insomnia disorder.¹³

An analysis by Public Health England analysis showed that, in 2017 to 2018, 1 million adults in England (2% of the adult population) received, and had been dispensed, one or more prescriptions for z-drugs and 1.4 million (3%) for benzodiazepines –drugs for treating insomnia. For benzodiazepines the indication included anxiety as well as insomnia. For the period prior to March 2018, 120,000, and 100,000 patients had received a continuous prescription for benzodiazepines and z-drugs respectively for at least 3 years. This may demonstrate the need for an alternative effective and safe treatment for insomnia.¹⁴

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For short-term insomnia, a short course (less than 2 weeks) of a hypnotic drug may be considered if daytime impairment is severe.⁷

For long-term insomnia, cognitive and behavioural interventions are recommended as first-line treatments:⁷

- A short course of a hypnotic drug may be considered for immediate relief or to manage an acute exacerbation of persistent insomnia.
- For older people (more than 55 years of age) with persistent insomnia following cognitive and behavioural interventions, modified-released melatonin is an option.
- Long term hypnotics and other sedative drugs, complementary and alternative therapies, and herbal remedies are not recommended.

Referral to a sleep clinic or a specialist with expertise in sleep medicine may be required if primary sleep disorder is suspected, there is doubt regarding the diagnosis, or long-term insomnia has not responded to management in primary care.⁷

CURRENT TREATMENT OPTIONS

Scenario: managing short-term insomnia (<4 weeks):⁷

- Advise patient on good sleep hygiene
- Short course of a hypnotic drug if daytime impairment is severe:
 - Short-acting benzodiazepines – temazepam, lorazepam, lormetazepam
 - Non-benzodiazepines (the ‘z-drugs’) – zopiclone, zolpidem, and zaleplon (all are short acting)
 - Diazepam is not generally recommended, but is useful if insomnia is associated with daytime anxiety
- Cognitive behavioural therapy if symptoms persist.

Scenario: managing long-term insomnia (>4 weeks):⁷

- Cognitive or behavioural intervention
- Advise patient on good sleep hygiene and regular exercise, in addition to cognitive or behavioural intervention
- For people with severe symptoms or an acute exacerbation of persistent insomnia, a short course of a hypnotic drug may be considered for immediate relief of symptoms
- Refer to sleep clinic or a specialist with expertise in sleep medicine if insomnia persists despite primary care management

PLACE OF TECHNOLOGY

Daridorexant is intended to be used as second-line treatment following cognitive or behavioural intervention in patients with insomnia.

CLINICAL TRIAL INFORMATION

Trial	NCT03545191 ; ID-078A301; Daridorexant (ACT-541468) vs placebo; Phase III Location(s): USA, Canada, Australia, Europe (excluding the UK)
Trial design	Randomised, multi-centre, double-blind, placebo-controlled trial
Status	Ongoing.
Population	N=900 (planned); male or female aged ≥ 18 years; insomnia disorder according to the DSM-5 criteria; Insomnia Severity Index score ≥ 15 ; Insufficient sleep quantity as collected subjectively in the sleep diary
Intervention(s)	Daridorexant, 25mg or 50mg, administered orally, once daily in the evening
Comparator(s)	Matched placebo
Outcome(s)	<p>Primary outcomes:</p> <ul style="list-style-type: none">• Change from baseline to Month 1 in Wake After Sleep Onset (WASO) (sleep maintenance)• Change from baseline to Month 3 in Wake After Sleep Onset (WASO)• Change from baseline to Month 1 in Latency to Persistent Sleep (LPS) (sleep onset)• Change from baseline to Month 3 in Latency to Persistent Sleep (LPS) <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Trial	NCT03575104 ; ID-078A302; Daridorexant (ACT-541468) vs placebo; Phase III Location(s): USA, Canada, Europe (excluding the UK)
Trial design	Multi-centre, double-blind, randomised, placebo-controlled trial
Population	N=900 (planned); male or female aged ≥ 18 years; insomnia disorder according to the DSM-5 criteria; Insomnia Severity Index score ≥ 15 ; Insufficient sleep quantity as collected subjectively in the sleep diary
Intervention(s)	Daridorexant, 25mg or 50mg, administered orally, once daily in the evening
Comparator(s)	Matched placebo
Outcome(s)	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Change from baseline to Month 1 in Wake After Sleep Onset (WASO) (sleep maintenance) • Change from baseline to Month 3 in Wake After Sleep Onset (WASO) • Change from baseline to Month 1 in Latency to Persistent Sleep (LPS) (sleep onset) • Change from baseline to Month 3 in Latency to Persistent Sleep (LPS) <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Trial	NCT03679884 ; ID-078A303; Daridorexant (ACT-541468) vs Placebo; Phase III extension Location(s): USA, Canada, Australia, Europe (excluding the UK)
Trial design	Multi-centre, double-blind, randomised, placebo-controlled trial
Population	N=1260 (planned); male or female aged ≥ 18 years; Having completed the DB study treatment and the run-out period of ID-078A301 or ID-078A302 (Visit 1); For woman of childbearing potential: Negative urine pregnancy test (EOT of ID-078A301 or ID-078A302 studies); Agreement to use the contraception scheme as required by the protocol from Visit 1 up to at least 30 days after EODBT
Intervention(s)	Daridorexant, 25mg or 50mg, administered orally, once daily in the evening
Comparator(s)	Matched placebo.
Outcome(s):	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Serious adverse events (SAEs) • Treatment-emergent adverse events (TEAEs) <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Trial	NCT02839200 ; AC-078A201; Daridorexant (ACT-541468) vs Zolpidem vs Placebo; Phase II trial Location(s): USA, Europe (excluding the UK)
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Trial design	Multi-centre, double-blind, randomised, placebo-controlled, active-reference trial
Population	N=360; male or female aged 18-64 years (inclusive); women of childbearing potential must have negative pregnancy tests and use reliable methods of contraception up to 30 days after EOT; $18.5 \leqslant \text{BMI} (\text{kg}/\text{m}^2) < 32$; Insomnia disorder according to DSM-5 criteria; Insufficient sleep quantity as collected subjectively in the sleep diary and validated objectively by polysomnography; Insomnia Severity Index score ≥ 15
Intervention(s)	Daridorexant, 5mg, 10mg, 25mg or 50mg, administered orally, once daily in the evening
Comparator(s)	Either: <ul style="list-style-type: none"> • Zolpidem, 10mg, administered orally as tablets once daily in the evening • Matched placebo
Outcomes(s)	Primary outcome: change in wake after sleep onset (WASO) from baseline to Days 1 and 2 [Time Frame: Baseline and Days 1&2] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Trial	NCT02841709 ; AC-078A202; Daridorexant (ACT-54168) vs Placebo; Phase II crossover trial Location(s): USA, Germany
Trial design	Multi-centre, double-blind, randomised, placebo-controlled, 5-period, 5-treatment crossover trial
Population	N=50; male or female aged ≥ 65 years; $18.5 \leq \text{BMI} (\text{kg}/\text{m}^2) < 32.0$; Insomnia disorder according to DSM-5 criteria; self-reported history of insufficient sleep quantity; insufficient sleep quantity as collected subjectively in the sleep diary and validated objectively by polysomnography; insomnia severity index score ≥ 15 .
Intervention(s) / Comparators:	Randomised to either: <ol style="list-style-type: none"> 1. Sequence 1 - On the evening of the first 2 days of each period they receive one dose (D) of ACT-541468 or placebo orally in the following order: D4, D2, D3, D1 and P, with D4 = the highest dose (50 mg) and D1 the lowest dose (5 mg). Each treatment period is separated from the next one by a 5- to 12- day washout. 2. Sequence 2 - Each subject participates in 5 treatment periods. On the evening of the first 2 days of each period they receive one dose (D) of ACT-541468 or placebo orally in the following order: D2, P, D4, D3 and D1, with D4 = the highest dose (50 mg) and D1 the lowest dose (5 mg). Each treatment period is separated from the next one by a 5- to 12-day washout. 3. Sequence 3 - Each subject participates in 5 treatment periods. On the evening of the first 2 days of each period they receive one dose (D) of ACT-541468 or placebo orally in the following order: D3, D1, D2, P and D4, with D4 = the highest dose (50 mg) and D1 the lowest dose (5 mg). Each treatment period is separated from the next one by a 5- to 12-day washout.

	<p>4. Sequence 4 - Each subject participates in 5 treatment periods. On the evening of the first 2 days of each period they receive one dose (D) of ACT-541468 or placebo orally in the following order: P, D4, D1, D2, D3, with D4 = the highest dose (50 mg) and D1 the lowest dose (5 mg). Each treatment period is separated from the next one by a 5- to 12-day washout.</p> <p>5. Sequence 5 - Each subject participates in 5 treatment periods. On the evening of the first 2 days of each period they receive one dose (D) of ACT-541468 or placebo orally in the following order: D1, D3, P, D4 and D2 with D4 = the highest dose (50 mg) and D1 the lowest dose (5 mg). Each treatment period is separated from the next one by a 5- to 12-day washout.</p>
Primary Outcomes	<ul style="list-style-type: none"> Change in wake after sleep onset (WASO) from baseline to Days 1 and 2 [Time Frame: Baseline, Day 1 and Day 2 of each treatment period] <ul style="list-style-type: none"> WASO is the time in minutes spent awake after onset of persistent sleep until lights on as determined by polysomnography (PSG)
Secondary Outcomes	<ul style="list-style-type: none"> Change in mean latency to persistent sleep (LPS) from baseline to Days 1 and 2 [Time Frame: Baseline, Day 1 and Day 2 of each treatment period] <ul style="list-style-type: none"> LPS is the duration of time in minutes from lights off to persistent sleep onset as determined by PSG
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Previously reported as June 2017.

ESTIMATED COST

The cost of daridorexant is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Guidance on the use of zazeprol, zolpidem and zopiclone for the short -term management of insomnia (TA77). April 2004.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS Southern Health. SH CP 136 Guidelines for Treatment of Primary Insomnia. October 2019.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Insomnia. April 2015.¹⁵
- European Medicines Agency. Guideline on medicinal products for the treatment of insomnia. February 2011.¹¹

ADDITIONAL INFORMATION

Idorsia Pharmaceuticals, Ltd. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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