Incannex

IHL-42X

for treatment of obstructive sleep apnoea

Phase II proof of concept clinical trial results.

ASX Ticker: IHL | NASDAQ Ticker: IXHL

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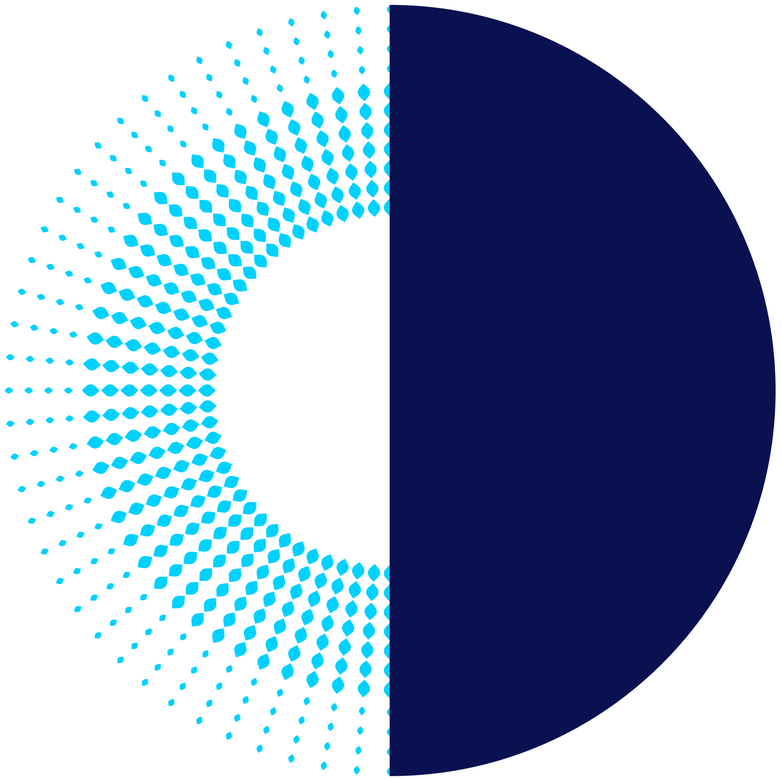
Company statement on clinical trial results

IHL42x has exceeded our expectations. It has shown substantial clinical benefit to people with obstructive sleep apnoea at the lowest dose given.

This not only means people can get the full benefit with a reduced risk of side effects, but also, during the low dose treatment period every subject was substantially below the legal driving limits for THC in their blood the morning after dosing, thus removing a significant hurdle for IHL-42X's widespread use.



Unmet Medical Need

Obstructive sleep apnoea ('OSA')

OSA involves the narrowing of the upper airway during sleep, which interferes with a person's breathing. Decreased oxygen uptake results in poor-quality sleep.

Untreated OSA leads to serious long-term adverse health outcomes including hypertension, cardiovascular disease, heart attack, cognitive impairments, anxiety and depression, irritability and daytime fatigue increasing the risk of accidents.

There are no pharmacotherapy (drug) treatments available to those afflicted. The current 'standard of care' is the Continuous Positive Airway Pressure (CPAP) machine, however, patient compliance to CPAP is low due to various factors related to patient discomfort.

Opportunity

IHL-42X Obstructive Sleep Apnea

Problem

OSA leads to serious long term adverse health outcomes but is also grossly undertreated. It is a highly prevalent condition and current treatment options (machines and devices) have poor patient compliance.

Solution

IHL-42X has two pharmaceutical ingredients (THC and Acetazolamide) that target different aspects of OSA. Combined, these ingredients create a synergistic therapeutic effect, reducing the effects of OSA with low doses of each compound, minimising potential side effects and satisfying THC limits for impaired driving.

No available pharmacotherapies

US$10B(1)
Addressable market

6.2%(1)
Annual Growth Rate

OVER 900M
people globally have sleep apnoea

(1) https://www.grandviewresearch.com/industry-analysis/sleep-apnea-devices-market

Clinical development status

Unblinded and confidential interim clinical data provided to the patent examiner.

Patent claims considered novel and inventive.

Asset	Preclinical	Australian Phase 2 POC	FDA Pre-IND	FDA IND	FDA bioequivalence study	FDA Phase 2	FDA Phase 3	Anticipated Milestones
IHL-42X Obstructive Sleep Apnea*								Proposed open IND Q4 2022

IHL-42X Development Progress

Milestones achieved

Completed proof of concept phase 2 clinical trial

- Results indicate that IHL-42X is effective at reducing AHI in patients with OSA and is well tolerated.
- IHL-42X also reduced oxygen desaturation index, and improved patient reported sleep quality and the number of awakenings during the night.
- The morning after dosing with low dose IHL-42X, THC levels in blood were below the prohibited limit for driving.

Feedback received from FDA at pre-IND meeting

- Incannex do not require animal studies to open IND
- Guidance was provided on the data that needs to be included in the IND application as well as design of pivotal clinical trials.

IHL-42X patent filed and international search report and opinion deemed key claims to be novel and inventive.

Opportunity

Key Observations from phase 2 clinical trial – patients treated and concept confirmed

01.

IHL-42X in low dose form outperformed medium and high dose with respect to sleep, THC clearance and safety.

02.

Low dose IHL-42X reduced average Apnoea Hypopnea Index ('AHI') by an average of 50.7% versus baseline; 25% of participants experienced greater than 80% reduction in AHI.

03.

In low dose IHL-42X samples, THC concentrations in blood were below the limits for impaired driving the morning after dose administration on night 7.

04.

No serious treatment emergent adverse events were reported during the clinical trial.

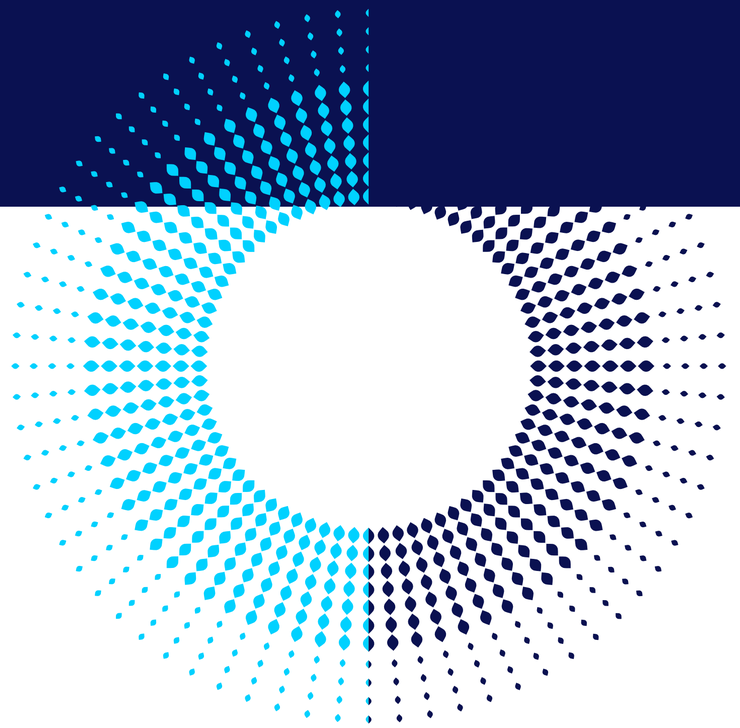
Apnoea hypopnea index (AHI) is the main measure for diagnosis and monitoring of disease, in patients with OSA. It is a serious sleep disorder in which breathing repeatedly stops and starts.

Strategic composition of dronabinol and acetazolamide makes IHL-42X an exciting novel potential treatment for OSA.

Low dose IHL-42X (2.5 mg dronabinol and 125 mg acetazolamide) reduced AHI to a greater extent than reported for its constituent pharmaceutical ingredients.
Low Dose IHL-42X was observed to reduce AHI by an average of 50.7%, indicating synergistic effect and a novel patent opportunity.

Dronabinol

- Synthetic form of (-)-trans-Δ9-tetrahydrocannabinol (THC).
- Approved in US for treatment of HIV/AIDS induced anorexia and chemotherapy induced nausea and vomiting.
- Dampens afferent vagal feedback, stabilizes respiratory patterns and dilates upper airway
- Two clinical trials to demonstrate effectiveness in reducing AHI in patients with OSA.
- AHI reduction with 2.5 mg dronabinol was 23.4 %.



Acetazolamide

- Carbonic anhydrase inhibitor.
- Used to treat glaucoma, altitude sickness, epilepsy and other indications.
- Increases the difference between prevailing PCO2 and apnoeic PCO2.
- Demonstrated as an effective treatment for OSA in 14 clinical studies.
- AHI reduction was 23.9-27.6% relative to baseline with 250 mg dose.

Clinical Trial

IHLOSAPOC1

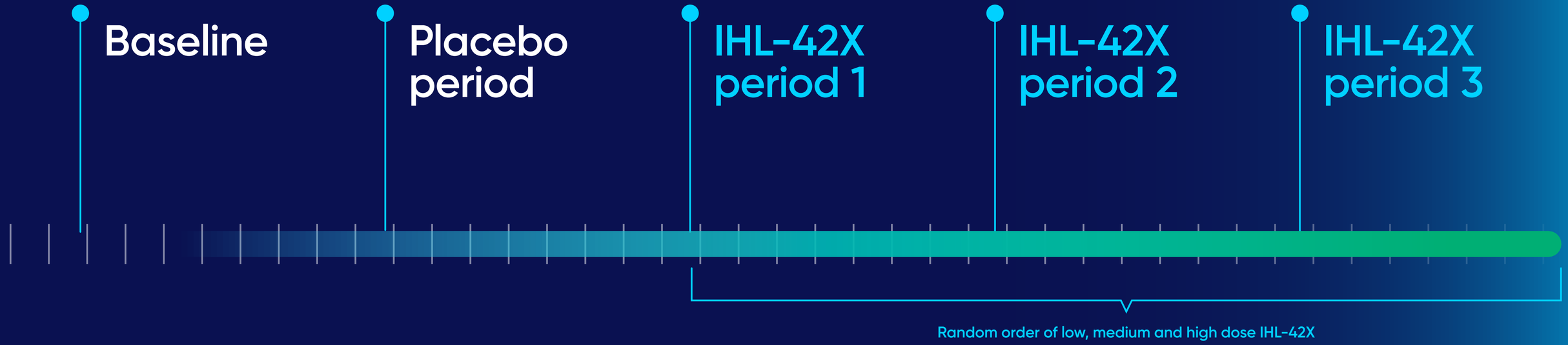
Incannex's proof of concept clinical trial to assess the safety and efficacy of IHL-42X in patients with OSA.

Compared three doses of IHL-42X to placebo at reducing AHI compared to baseline (primary endpoint).

Other assessments included:

- Oxygen desaturation index
- Plasma THC levels
- Patient reported sleep quality
- Sleep metrics captured by actigraphy
- Safety

Study Design



Observation

- Four period cross over study.
- Participants had OSA confirmed at baseline, once eligibility was confirmed they completed a single blind placebo treatment period followed by three double blind IHL-42X treatment periods.
- Each treatment period was seven days with an overnight sleep study on night seven to determine AHI and collect secondary endpoint data.
- Treatment periods were separated by seven-day washout periods.
- Adverse events were recorded and monitored for the duration of the study.

Participant demographics

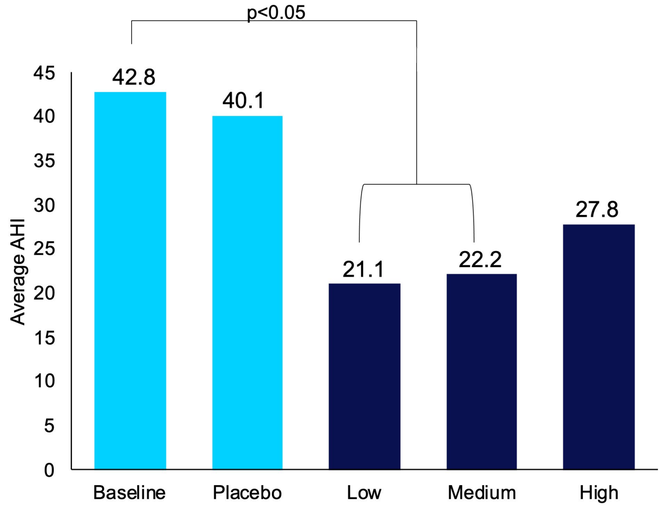
Demographic	Results (Mean (Range))
Age	51.82 (39-64)
Sex (female)	3/11
Childbearing Potential (Yes)	1/11
Race	10 White, 1 Asian
Ethnicity	Not Hispanic or Latino 100%
Height (cm)	178.16 (160-187.3)
Weight (kg)	92.23 (66.8-117)
BMI	28.93 (24.9-36.9)
Education (coded from 1-6)*	3.73 (1-6)
Marital Status	5 Married, 1 Never Married, 3 Divorced, 2 Domestic Partner
Handedness (Right)	10/11
English as Native Language (Yes)	10/11
AHI at baseline	42.8

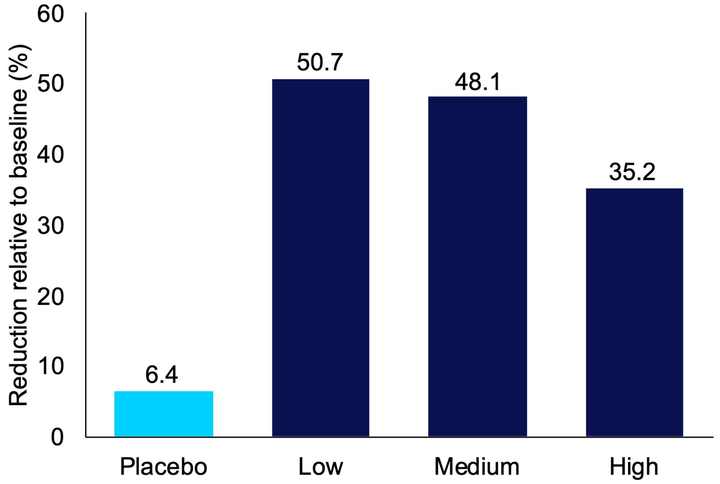
**Education was coded with the following: 1 = 9th Grade; 2 = 12th Grade Diploma or GED; 3 = Some College, No Degree; 4 = Academic Associate Degree; 5 = Bachelor's Degree; 6 = Master's Degree*

Results

IHL-42X ⟶ reduced AHI at a group level.

- Low dose IHL-42X was the most effective dose strength with an average reduction in AHI of 50.7% compared to the baseline.
- When comparing the means of the treatment groups, the difference observed for both low and medium dose compared to baseline was statistically significant ($p<0.05$).

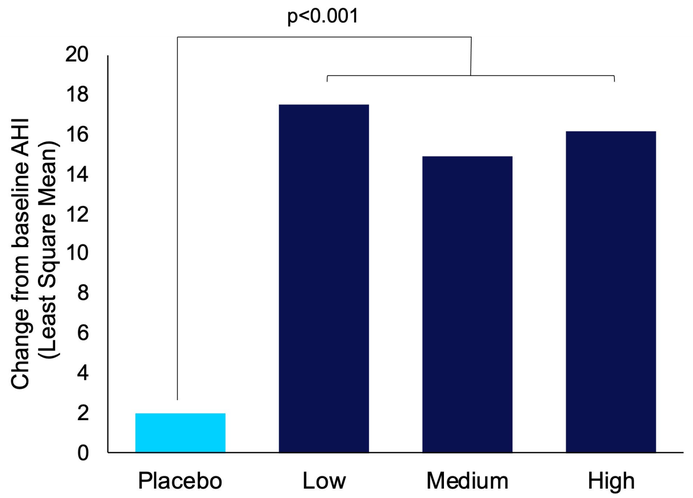


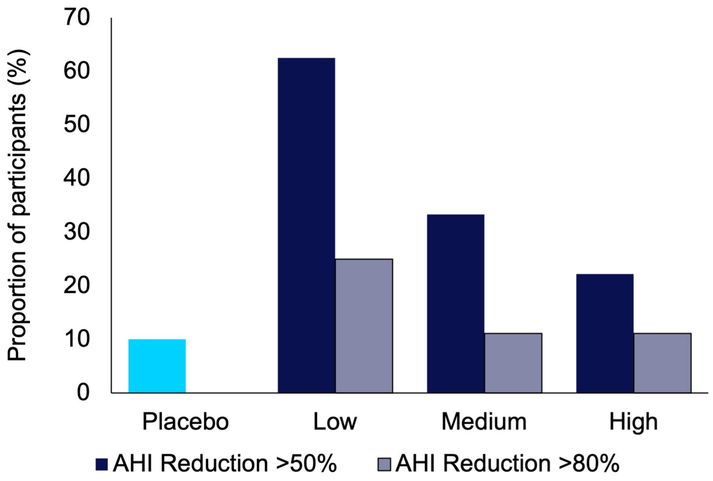


Results

IHL-42X ⟶ reduced AHI when compared within participants.

- 25% of participants experienced greater than 80% reduction in AHI.
- All three doses of IHL-42X led to a statistically significant (p<0.001) reduction in AHI compared to placebo when calculated directly to each participant's baseline.
- Low dose IHL-42X treatment led to a reduction relative to baseline in AHI of >50 % in 62.5% of participants and >80% in 25% of participants.





Summary of AHI data

During IHL-42X treatment periods AHI was reduced compared to baseline and placebo treatment periods.

- This means that when treated with IHL-42X, the subjects' breathing was interrupted less frequently during sleep.
- This supports Incannex's hypothesis that IHL-42X is an effective treatment for OSA.

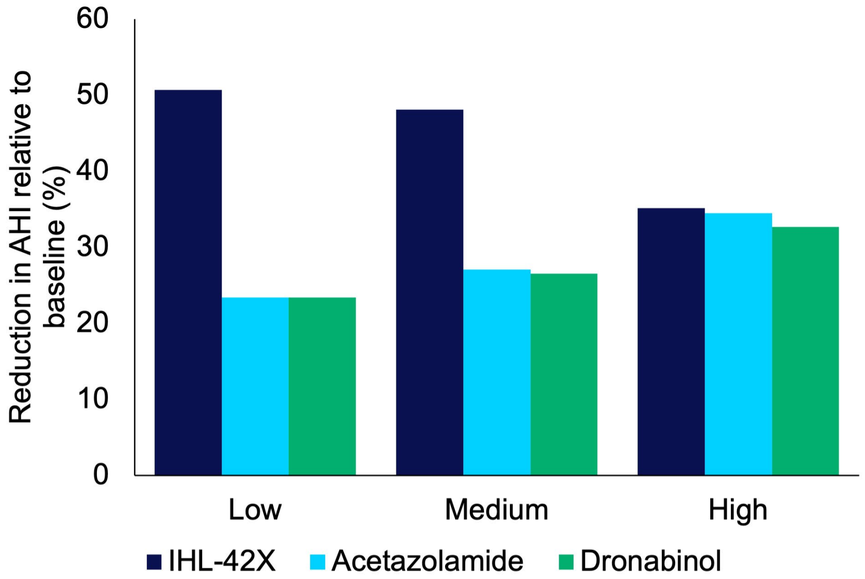
Low dose IHL-42X was more effective at reducing AHI than either the medium or the high dose.

- This is encouraging for Incannex's development of IHL-42X as a lower dose will reduce the risk of side effects and the cost of goods.

Results

IHL-42X ⟶ reduced AHI to a greater extent than reported for acetazolomide and dronabinol as monotherapies.

– IHL-42X at a low and medium dose reduce AHI to a greater extent relative to baseline than acetazolamide (1) and dronabinol (2) at equivalent doses (based on extrapolation of published data with linear dose response curves with R2 values of 0.93 and 1 for acetazolomide and dronabinol respectively).



1. Schmickl CN,et. al. 2020. Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. Chest 158:2632–2645.
2. Carley DW,et. al. 2018. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: Effects of dronabinol in obstructive sleep apnea. Sleep 41

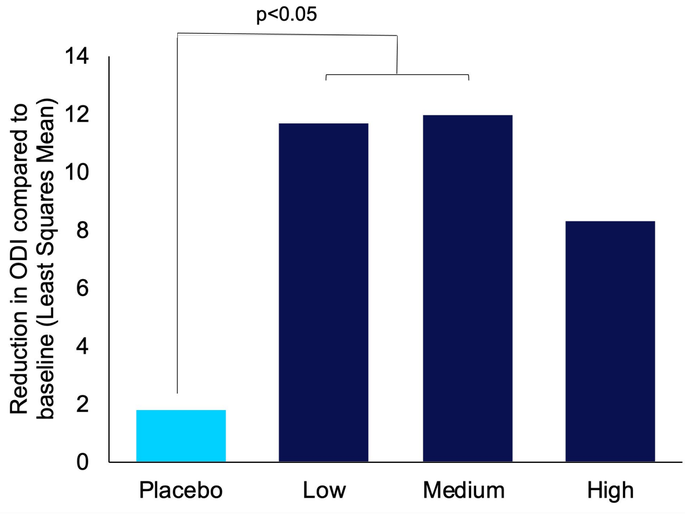
Summary of comparison with dronabinol and acetazolamide

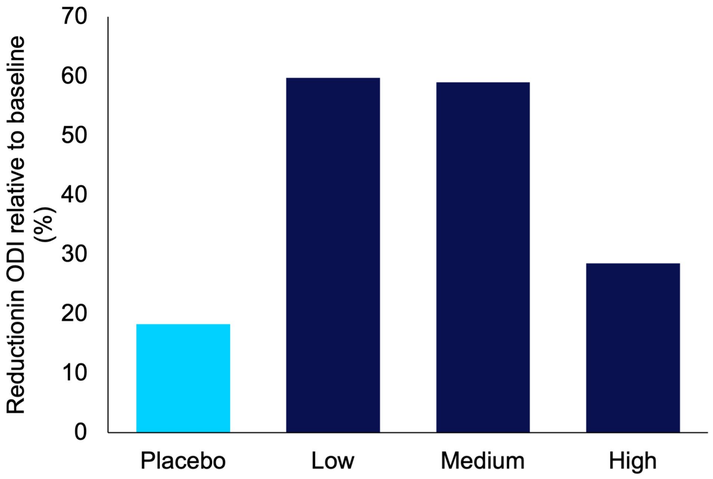
Low and medium dose IHL-42X reduced AHI to a greater extent than reported for dronabinol and acetazolamide monotherapies at equivalent doses.

- This supports Incannex's hypothesis that dronabinol and acetazolamide are acting synergistically to treat OSA.
- This data provides Incannex with confidence that IHL-42X will meet the FDA's combination rule where both APIs must contribute to the therapeutic effect of a fixed dose combination product.
- This supports Incannex's hypothesis that IHL-42X is an effective treatment for OSA.

IHL-42X ⟶ reduces oxygen desaturation index (ODI).

– IHL-42X at a low and medium dose led to reduction in ODI of 59.7 and 59.0% respectively. These reductions were statistically significant (p<0.05).





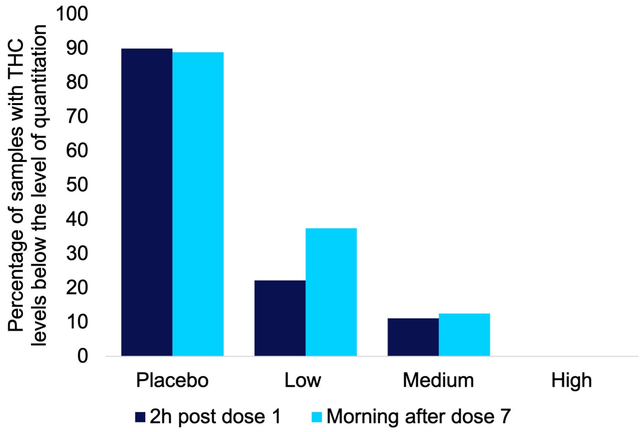
Summary of ODI data

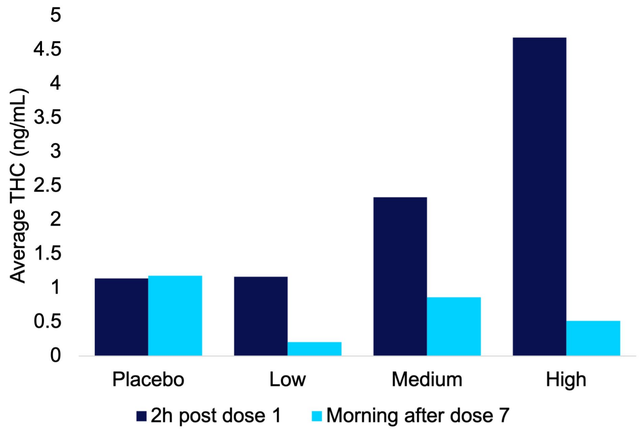
Low and medium dose IHL-42X significantly reduced oxygen desaturation index during sleep.

- This means that during low and medium dose IHL-42X treatment, subjects had more oxygen in their blood
- Low oxygen saturation, or high oxygen desaturation, can lead to:
  - *oxidative stress which can damage cells and tissues*
  - *bursts of the stress hormone cortisol*
  - *insulin resistance and increased risk of diabetes*
  - *altered metabolism*
  - *Increased risk of cardiovascular disease*

Results

THC clearance





- THC levels in blood samples collected the morning after dose 7 were below the limit of detection (0.1 ng/mL) in 37.5 % of low dose IHL-42X samples.
- The average THC concentration in blood samples from the morning after night 7 in the low dose IHL-42X treatment period was 0.20 ng/mL.
- The highest THC concentration detected in a sample from the low dose group was 0.45 ng/mL.

Country	THC blood concentration above which driving is prohibited
Canada[1]	2 ng/mL
Norway[2]	1.3 ng/mL
UK[3]	2 ng/mL
Ireland[4]	1 ng/mL
Germany[4]	1 ng/mL

1. https://www.justice.gc.ca/eng/cj-jp/sidl-rlcfa/qa2-qr2.html

2. Vindenes, V., et al., (2012) Impairment based legislative limits for driving under the influence of non-alcohol drugs in Norway, Forensic Science International 219(1-3,)1-11

3. Wolff, K, et al., Driving Under the Influence of Drugs: Report from the Expert Panel on Drug Driving, Department of Transport, London, 2013.

4. https://www.vifm.org/wp-content/uploads/VIFM-Annual-Report-2019-2020.pdf

Summary of THC clearance

Countries that have levels of THC in blood above which driving is prohibited have set limits at 1-2 ng/mL.

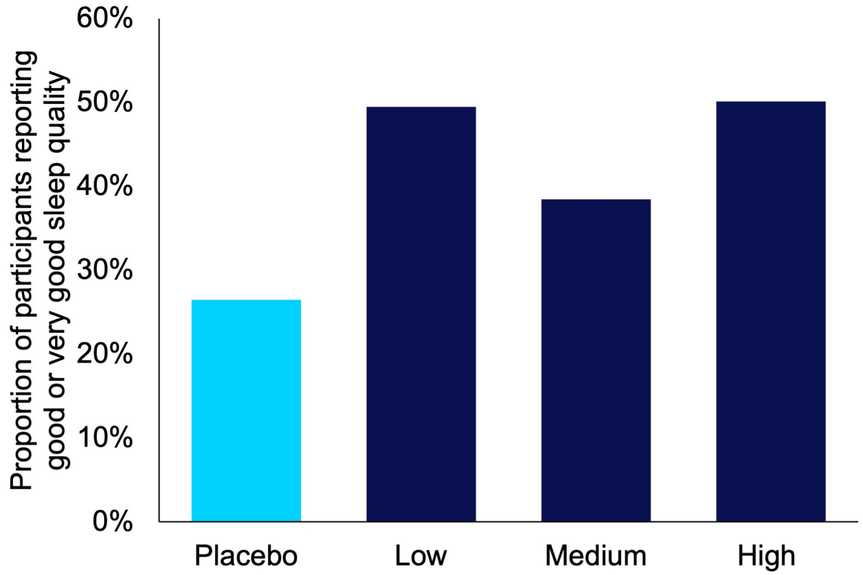
The morning after low dose IHL-42X 37.5% of subjects had no detectable THC in their blood.

In the low dose blood samples that did have detectable THC the average concentration was 0.20 ng/mL and the maximum was 0.45 ng/mL, both of which are below the permissible limits.

The THC clearance data indicates that low dose IHL-42X is unlikely to pose a risk for patients to legally drive while using the drug to treat their sleep apnoea.

IHL-42X ⟶ improved patient reported sleep quality.

- Participants recorded their sleep quality or satisfaction every night through out the study as very poor, poor, fair, good or very good.
- During IHL-42X treatment periods, the percentage of participants that ranked their sleep as good or very good was increased, compared to placebo. This is an average across the seven nights of each treatment period, for all the participants.



1. Schmickl CN,et. al. 2020. Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. Chest 158:2632–2645.
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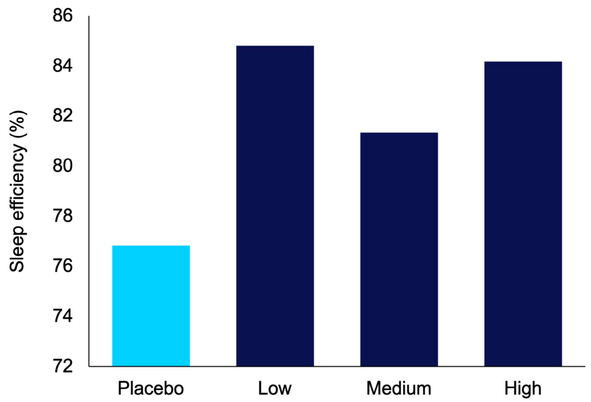
Results

IHL-42X ⟶ improved sleep metrics captured by actigraphy (wearable sleep monitor).

(1)



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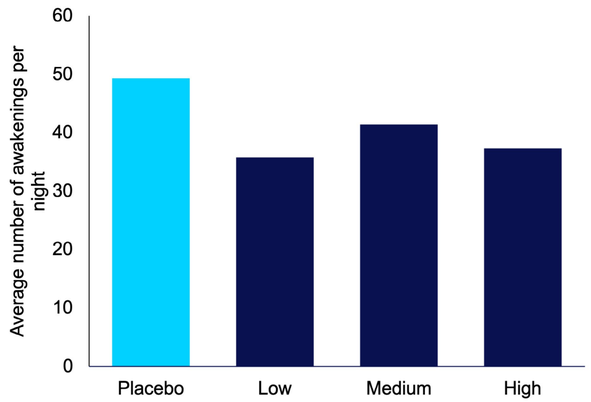

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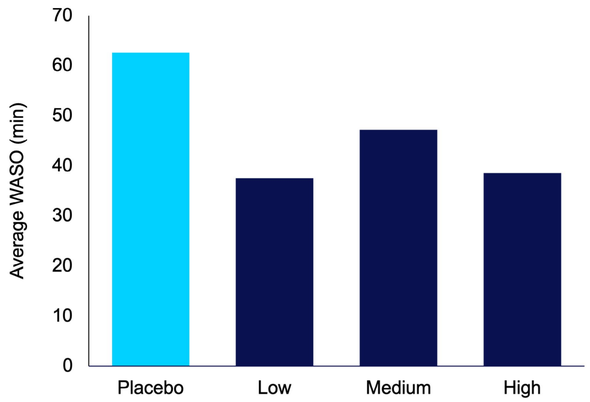


During IHL-42X treatment periods, subjects were asleep for a greater proportion of their time in bed (sleep efficiency)

(1) woke up fewer times

(2) and were awake for less time (wake after sleep onset (WASO)

(3) than during the placebo treatment period.

Summary of sleep quality

During IHL-42X treatment periods subjects reported a higher level of sleep satisfaction than placebo periods.

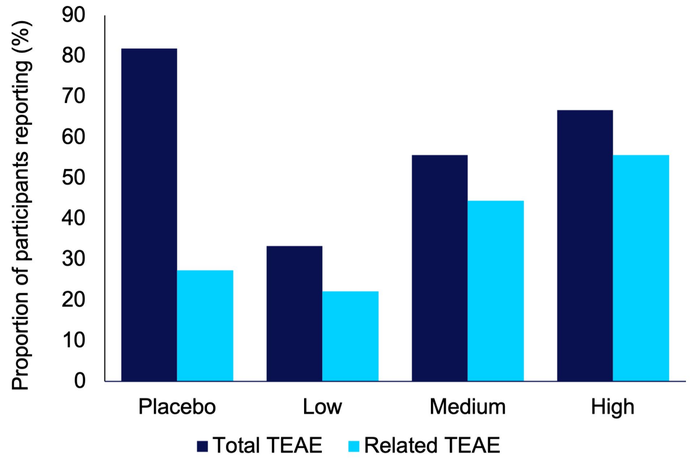
Data from the Actiwatch indicated that subjects were sleeping through the night better than during the placebo period.

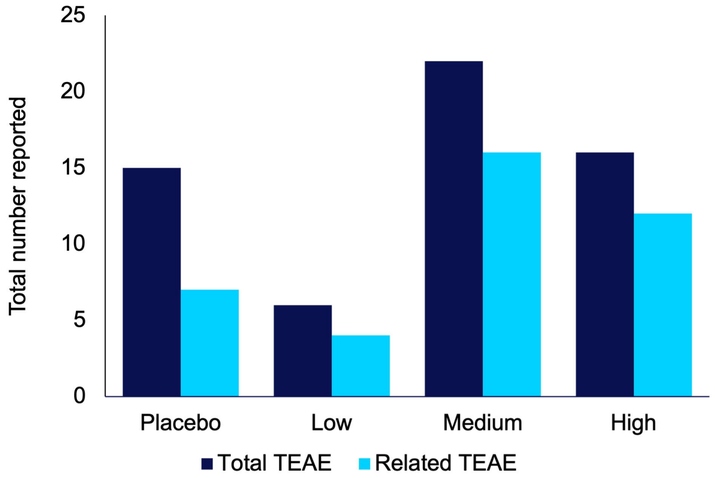
These data support that IHL-42X improved sleep quality, despite a lack of improvement in secondary endpoints that focused on sleepiness, mood and quality of life.

Results

IHL-42X ⟶ was well tolerated.

- No serious treatment emergent adverse events (TEAE) were reported during the study.
- Low dose IHL-42X had the lowest proportion of participants reporting TEAEs and the fewest number of total TEAEs compared to other treatment groups.
- One participant on high dose IHL-42X had a TEAE that caused them to be withdrawn from the study. However, they tested positive for illicit substances other than cannabis.
- One participant on placebo had a severe TEAE that was not linked to the study drug.





Safety summary

IHL-42X was well tolerated across all three dose levels.

- No serious adverse events (side effects) were reported during the study.
- The only severe adverse event was reported during the placebo treatment period and was not linked to the study drug.

Adverse event rates during the low dose IHL-42X treatment period were lower than even placebo.

These results support Incannex's hypothesis that combining dronabinol and acetazolamide into IHL-42X will reduce the potential for side effects.

Results

Conclusions

01.

Data from phase 2 proof of concept clinical trial supports the potential of IHL-42X as an effective and well tolerated treatment for OSA, meeting the unmet needs of millions of people.

02.

IHL-42X reduced AHI, improved sleep quality with respect to both patient reported outcome and actigraphy, and did not lead to any adverse events beyond those expected based on what was expected from dronabinol and acetazolamide.

03.

Low dose IHL-42X was the most effective of the doses tested in this study.

- It reduced AHI by over half (on average) in trial participants and 25% of participants saw an 80% reduction in AHI.
- Low dose IHL-42X has the lowest number of reported adverse events, even lower than placebo.
- Low observed THC blood concentration amongst participants below limits for impairment to drive.

04.

Patent application for IHL-42X considered “novel and inventive” by international patent examiner.

05.

Pre-IND meeting completed with FDA and the next major development milestone for IHL-42X will be the commencement of the IND opening clinical trial.

Acknowledgments

Dr Jen Walsh and the team at UWA Centre for Sleep Science for work as a clinical trial site.

Prof Terry O’Brien and the team at The Alfred for work as a clinical trial site.

Novotech for managing the trial and study data.

Agilex for analysis of samples for THC and metabolite levels.

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