ZENIVOL® improves Insomnia Severity Index (ISI) scores and is well tolerated in the real-world setting

Authors

Dr Meghan Thomas
Vice President Clinical Programs and Operations, Zelira Therapeutics, Perth, Australia

Prof Christopher Frampton
Department of Medicine, University of Otago, Christchurch, New Zealand

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Zelira® Therapeutics Ltd

Background

As a sponsor of unregistered medicinal cannabis products in Australia, Zelira Therapeutics is responsible for approving the dispensing of each bottle to the patient.[1,2]

An essential part of improving the quality of care of patients is to understand how they are using Zelira products on the assumption that they are dosing to achieve clinical efficacy.

By understanding how patients are using Zelira products in the real-world setting, this information can be provided to clinicians and patients to support their journey of achieving clinical improvement.

What is ZENIVOL®?

ZENIVOL® is Zelira's proprietary formulation of THC, CBD and CBN that was used in a world-first randomised, double-blind placebo-controlled crossover trial of 24 participants with chronic insomnia. Results from the trial were published in the peer reviewed journal SLEEP[3] and demonstrated that following 2 weeks of treatment with ZENIVOL® patients saw a significant decrease in insomnia symptoms relative to placebo. An increase in adverse events was reported while taking ZENIVOL® compared to the placebo, however all were mild and the majority were considered transient resolving soon after waking. Following the trial the investigators concluded that ZENIVOL® may provide a useful therapeutic option for individuals with chronic insomnia, at least for short term use.

Following the successful completion of the trial in September 2020, Zelira Therapeutics launched ZENIVOL® to Australian patients under the Therapeutic Goods Administration's (TGA) Special Access Scheme B and the Authorised Prescriber Scheme.

ZENIVOL® is a tincture blended with pharmaceutical grade sunflower oil. It is a 20:2:1 THC:CBN:CBD ratio with 20mg/mL of THC, 2mg/mL CBN and 1mg/mL of CBD. As a high THC product, the TGA categorised ZENIVOL® as a Category 4 (THC dominant) product.

ZENIVOL® is taken sublingually. Based on the clinical trial data currently available, patients should take 0.5mL (10mg of THC) of ZENIVOL® 1-2 hours before bedtime. If required, the dose can be increased to 1mL (20mg of THC).

Dataset and analysis

The analysis in this paper is drawn from two independent sources namely the Zelira dispensing database and patient data captured by Emyria through their Emerald Clinics located in Western Australia (West Leederville), Victoria (Balwyn), and New South Wales (Sydney, Alstonville, Goonellabah) using a bespoke data platform that gathers ethically-sourced clinical evidence from their patients.

The Zelira dispensing database was commissioned by Zelira and is a cloud based electronic database that enables the request (by the pharmacist) and approval (by Zelira) of a dispense with the appropriate approval documentation (i.e. Special Access Scheme B approval letter, Authorised Prescriber Scheme approval letter).

The first 94 ZENIVOL® dispenses were analysed in this paper. As dispenses are continually occurring, patients were classified as active, lapsed or new. A lapsed patient was defined as not having received any product within the 4 month period prior to the data extraction date. New patients were defined as those having received at least a single bottle within the last 4 months of the data extraction date. All others were considered active.

More detailed data was captured on a subset of patients with insomnia (n=42) that were dispensed ZENIVOL® and that attended an Emerald Clinic. Dosing information (time of day, amount), demographics, adverse events and concomitant medications were collected. All patients that attend an Emerald Clinic are asked to complete a standard set of questionnaires, including the Insomnia Severity Index (ISI) at their initial consultation with an Emerald doctor and at follow up appointments. The ISI has seven questions which patients are asked to rate their current (i.e. last 2 weeks) severity. The seven answers are added to give a total score with a higher score indicating more severe insomnia:

No clinically significant insomnia (0–7)
Subthreshold insomnia (8–14)
Clinical insomnia (moderate severity) (15–21)
Clinical insomnia (severe) (22–28)

Not all patients that attended an Emerald Clinic were initially prescribed ZENIVOL®, and some patients switched products multiple times over an extended period of time. What has been analysed here are those patients that presented at an Emerald Clinic with an ISI score of at least eight (subthreshold insomnia) and that took ZENIVOL® at some point in their medicinal cannabis journey.

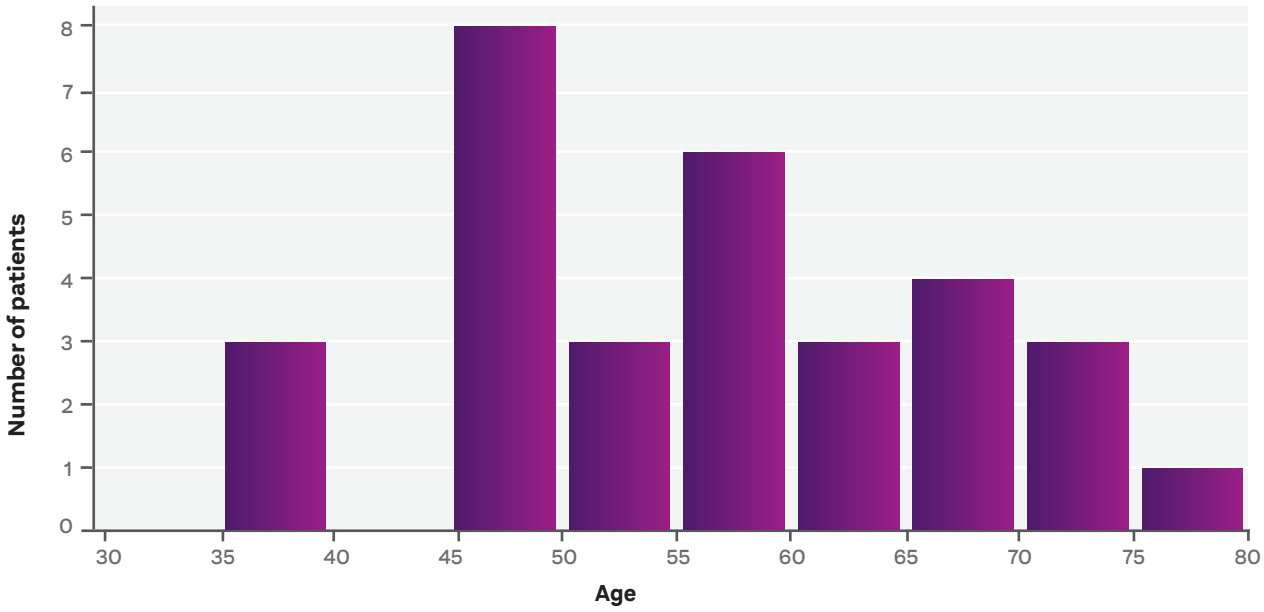
Results

Of the first 94 patients who were dispensed ZENIVOL®, a third were active patients (n=31, 33%), just over a third were new patients (n=35, 37%) and lapsed patients made up the remaining 30% (n=28).

Across Australia, the primary indication for which ZENIVOL® was prescribed was for Insomnia/Sleep Disorder followed by Chronic Pain. Of those doctors who prescribed ZENIVOL®, the majority (77%) were registered as General Practitioners, followed by Medical practitioners (13%), Psychiatrists (7%) and lastly, Respiratory and Sleep Medicine specialists (3%).

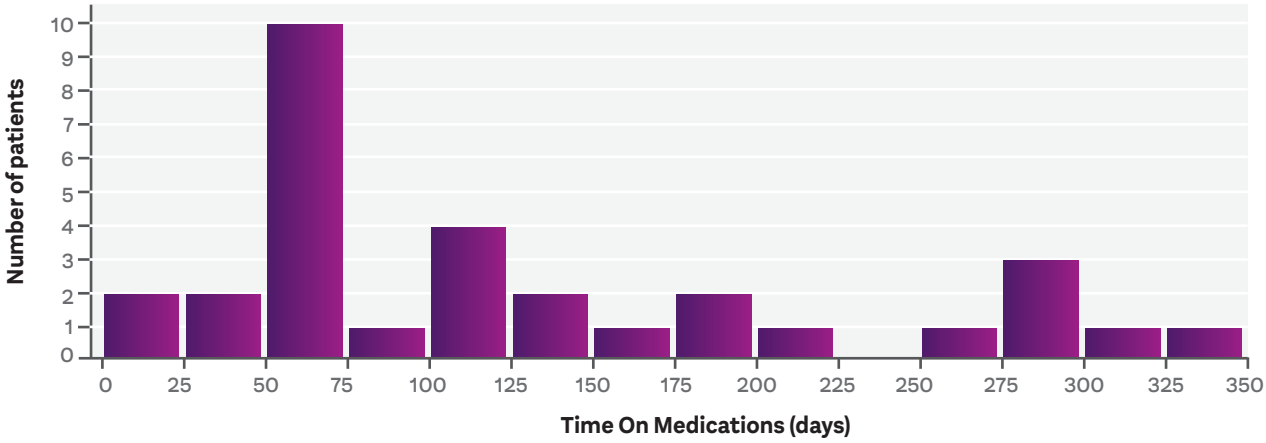
The mean age of active patients was 56 years of age with the oldest patient being 77 years of age **(Fig. 1)**. A substantial number of active patients (n=10, 32%) were 65 years of age or older. Those who did not continue taking ZENIVOL® were slightly younger with a mean age of 53 years.

Figure 1: Distribution of the ages of patients actively using ZENIVOL®



Of the active patients, the maximum time to-date that a patient had taken ZENIVOL® was 10.8 months (or 329 days) **(Fig. 2)**. The mean time on treatment for active ZENIVOL® patients was 4.3 months.

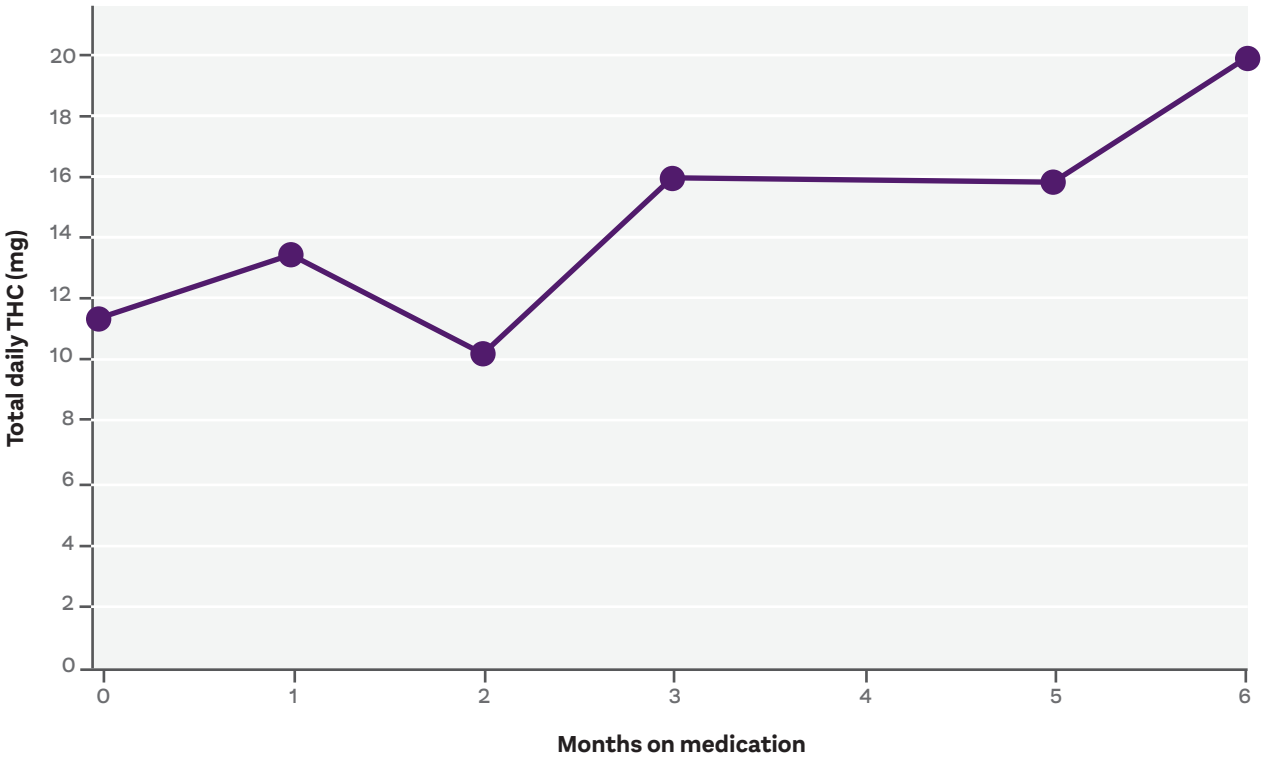
Figure 2: Distribution of the time ZENIVOL® active patients were on treatment



Of the first 94 patients who were dispensed ZENIVOL®, 42 attended an Emerald Clinic and had a baseline ISI score greater than eight (i.e. at least rated as having subthreshold insomnia) and 29 of these also had a follow up ISI score whilst on ZENIVOL®. The primary indications that these 29 patients presented to an Emerald Clinic with was for: Chronic non-cancer pain (44%), followed by Insomnia (36%) and post-traumatic stress disorder (12%). The mean age of Emerald ZENIVOL® patients was 54 years (range: 6–78 years of age).

Emerald patients on ZENIVOL® did not appear to dose escalate. Rather as per the instructions from the phase I/IIa clinical trial patients started on 0.5mL (10mg THC: 1mg CBN: 0.5mg CBD) with a few patients increasing the doses between 0.75mL to 1mL (20mg THC: 2mg CBN: 1mg CBD) after 3 months on treatment **(Fig. 3)**. Patients typically took ZENIVOL® at bedtime or in the evening.

Figure 3: Average total daily THC dose of Emerald Clinics ZENIVOL® patients



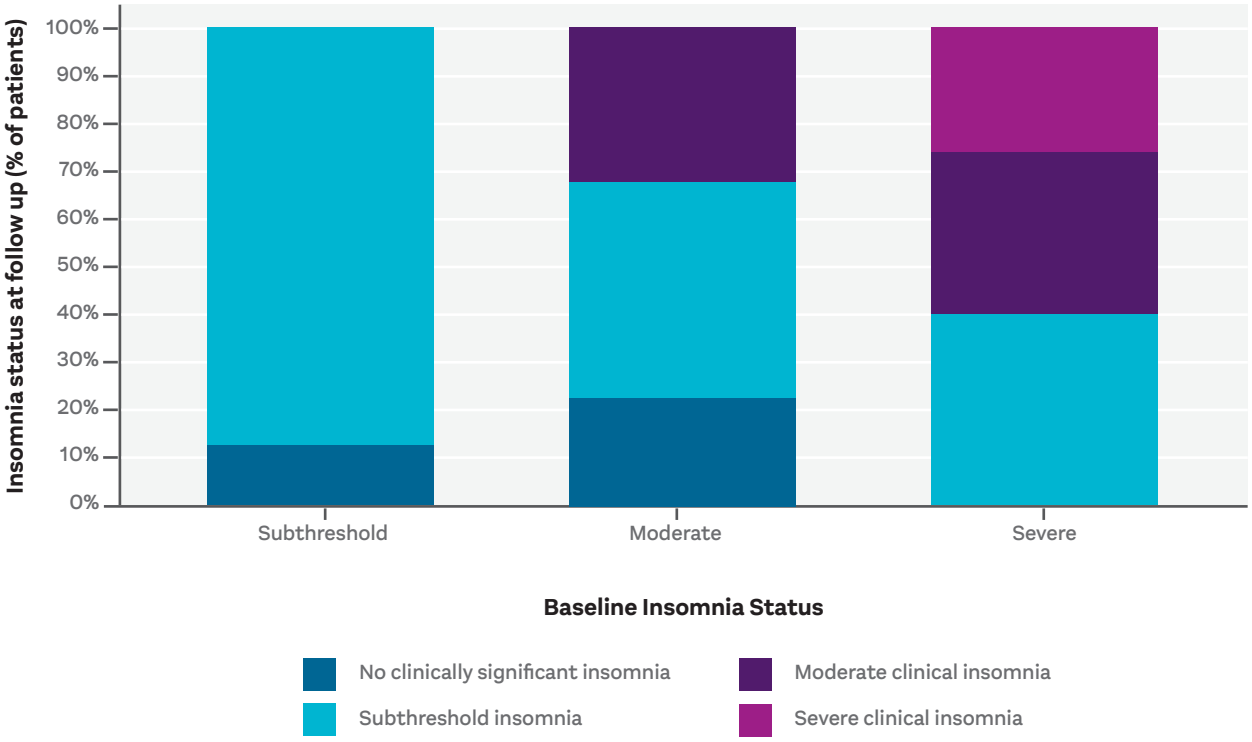
Overall, patients had a mean baseline ISI score of 19.5 *(Moderate clinical insomnia)*, however after taking ZENIVOL® the mean ISI score significantly reduced to 14.3 *(Subthreshold insomnia levels)* ($p<0.001$).

More specifically, at baseline, 15 patients were rated as having *Severe clinical insomnia*. After being on ZENIVOL®, 33% of the *Severe clinical insomnia* patients had reduced their ISI score to *Moderate clinical insomnia* levels, and 40% had reduced to *Subthreshold insomnia* levels. No improvement in the ISI score was seen in 27% of the *Severe clinical insomnia* patients (**Fig. 4**).

At baseline, nine (9) patients were rated as having *Moderate clinical insomnia*. After being on ZENIVOL®, a third saw no improvement in their insomnia, whilst 44% reduced their ISI score to *Subthreshold insomnia* levels and 22% achieved ISI scores that rated them as having *No clinically significant insomnia* **(Fig. 4)**.

For those patients with *Subthreshold insomnia* at baseline, 20% were able to reduce their ISI scores to *No clinically significant insomnia*, with the remainder maintaining a *Subthreshold insomnia* rating **(Fig. 4)**.

Figure 4: Change in insomnia status whilst on ZENIVOL®, as measured by the Insomnia Severity Index (ISI)



As expected for the Emerald Clinics ZENIVOL® patients, most reported being on a concomitant medication for pain relief ranging from opioids (i.e. oxycodone, codeine, tramadol), to benzodiazepines (diazepam) to over-the-counter pain relief medications (i.e. paracetamol, ibuprofen).

Conclusions

ZENIVOL® is a high THC product containing 20mg/mL of THC, 2mg/mL of CBN and 1mg/mL of CBD.

While the trial participants used ZENIVOL® for only two weeks, it is clear that in the Australian real-world setting patients are using ZENIVOL® for considerably longer periods.

A substantial proportion of active ZENIVOL® patients were over the age of 65 suggesting that in the short to medium term, ZENIVOL® is safe and effective in this cohort.

As expected, patients largely took 0.5mL (10mg THC: 1mg CBN: 0.5mg CBD) in the evening or before bed. This is in keeping with the currently available clinical trial evidence where patients took one dose (0.5mL) of ZENIVOL® 1 to 2 hours before bed.

Importantly, ZENIVOL® was effective at reducing insomnia symptoms; from *Moderate* to *Severe clinical insomnia* to S*ubthreshold* or N*ot clinically significant levels of insomnia*.

Taken in conjunction with the clinical trial results, the real-world data supports the use of ZENIVOL® as a useful therapeutic option for individuals (both adults and older adults) to manage chronic insomnia symptoms.

Patient Feedback

"I was taking over 10 medications, including anti-depressants, sleeping tablets and pain killers. This medication cocktail caused terrible side effects. ZENIVOL® has helped immensely...I'm no longer waking over 100 times a night, and it has helped to relieve some pain caused by a biking accident. ZENIVOL® has given me the opportunity to live life as a normal person again and enjoy things I was not able to previously...I am so grateful."

References

1. Therapeutic Goods Regulations 1990, Schedule 5A, Items 1 and 2.
2. TGA Guidance document: Importation, manufacture and supply of unapproved medicinal cannabis products, 19 November 2021. Available **here**.
3. Jennifer H Walsh, Kathleen J Maddison, Tim Rankin, Kevin Murray, Nigel McArdle, Melissa J Ree, David R Hillman, Peter R Eastwood, Treating insomnia symptoms with medicinal cannabis: a randomized, crossover trial of the efficacy of a cannabinoid medicine compared with placebo, Sleep, Volume 44, Issue 11, November 2021, zsab149, https://doi.org/10.1093/sleep/zsab149.