ASX Release

Zelira's Phase 1 Dose Escalation Study in Chronic Pain Patients on Long-Term Opioid Treatment Meets Primary and Secondary Endpoints

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- **Zelira successfully completed a Phase 1 dose escalation study to assess the safety of its cannabis formulation (ZTL-103) in seven chronic pain patients already using high doses of opioids.**
- **ZTL-103 treatment was well tolerated with no serious adverse events**
- **Treatment associated with dose-responsive improvement in subjective measures of pain, stress, anxiety and depression**
- **Supporting pharmacokinetic analysis informs dosing and safety**
- **Expands Zelira's leading portfolio of cannabinoid products supported by clinical data**
- **Supports Zelira's position as a global leader in the development of cannabinoid-based therapies to treat chronic pain**

Zelira Therapeutics Ltd (**ASX:ZLD, OTCQB:ZLDAF**), a global leader in the development of clinically validated cannabis medicines, has received the final clinical report for its Phase 1 dose escalation trial in chronic pain patients on long-term high-dose opioid treatment. Zelira is pleased to confirm the trial successfully met its primary and secondary endpoints for safety and efficacy.

The study was undertaken at the St Vincent's Hospital in Melbourne in conjunction with Emerald Clinics Ltd (ASX: EMD) in Perth who were engaged as a second site. The trial was led by coordinating principal investigator Associate Professor Yvonne Bonomo for St Vincents and Associate Professor Alistair Vickery for Emerald Clinics.

The phase 1 dose-escalation trial was designed to assess the safety of Zelira's cannabis formulation (ZTL-103) in chronic pain patients already on long-term high-dose opioid treatment. Nine patients were enrolled and seven patients completed the study. The mean age was 58 years and mean oral Morphine

Equivalent Daily Dose (oMEDD) was 93mg per day. Participants had a range of physical comorbidities and polypharmacy.

Patients were treated with a single sublingual dose of ZTL-103 containing 5 mg of total cannabinoids (2.5 mg THC and 2.5 mg CBD) on the first day. After a seven day washout they received another single dose of ZTL-103 containing 5 mg of total cannabinoids at the same time as having a high fat meal. Patients then continued to take two daily doses of 5mg of total cannabinoids for seven days, before escalating to 20 mg total cannabinoids per day for seven days and then up to 30 mg total cannabinoids for a further seven days before taking a single dose of 25 mg total cannabinoids. Patients then underwent a 7 day washout period before returning for the final study visit.

Primary Endpoints Achieved:

ZTL-103 is safe

- No serious adverse events reported
- Non-serious adverse events were mild and transient
- Maximal dose was generally well tolerated

Secondary Endpoints Achieved

Pharmacokinetic Analysis:

- Provided details regarding the rate of cannabinoid uptake into the body after dosing.
- Outcome helps inform dosing strategy to maximise safety and efficacy.

ZTL-103 Treatment Improved Subjective Measures of Pain

- Patient-reported impact of ZTL-103 treatment on pain assessed using Brief Pain Inventory (BPI) questionnaire. The BPI measures Pain Severity and Pain Interference (i.e. how pain impacts function and daily life).
- Pain interferences scores showed a dose responsive and statistically signficant reduction at daily doses ≥10 mg of total cannabinoids ($p=0.043$: p values ≤0.05 are considered statisically significant).
- There was no significant change in pain severity scores.

ZTL-103 Treatment Improved Subjective Measures of Anxiety, Stress and Depression

- Patient-reported impact of ZTL-103 treatment on anxiety, stress and depression assessed using DASS21 questionnaire.
- ZTL-103 treatment was associated with statisically significant reductions in scores for anxiety, stress and depression at daily doses ≥ 30 mg total cannabinoids (depression: $p=0.002$, anxiety: $p = 0.007$, stress: $p=0.03$).

- ZTL-103 treatment reduced median scores from 'Severe/Moderate' to 'Mild/Normal' category for anxiety, stress and depression at daily doses ≥ 10 mg total cannabinoids.

Prescription opioids for treating chronic pain are linked to serious side effects including physical dependence, which is an acknowledged growing global crisis. In the United States an estimated 49,000 people died from opioid overdose in 2017.

Associate Professor Yvonne Bonomo, **Coordinating Principal Investigator** for the study, and Director of the Department of Addiction Medicine, St Vincent's Hospital Melbourne said "*This trial showed that ZTL-103 treatment was safe and well-tolerated in patients diagnosed with chronic pain who were also taking high oMEDD doses. This is an encouraging outcome given that treatment of chronic patients is often complicated by the number of different concurrent medications they can be taking to treat a range of underlying conditions."*

"We were also pleased to observe positive efficacy signals for patient-reported pain, stress, anxiety and depression following treatment, which are all measures that impact patient well-being. These results would certainly warrant further clinical investigation to assess the ability of ZTL-103 therapy to reduce opioid dependence and improve pain and quality of life in chronic pain patients."

Associate Professor Alistair Vickery, **Principal Investigator** for the study, and **Medical Director** of Emerald Clinics said "*We are thrilled that our unique outpatient CRO capabilities could help support this phase 1 study and demonstrate that patients managed at home with complex chronic pain conditions and concomitant polypharmacy not only benefit from ZTL-103 but have only few minor adverse events or drug interactions."*

Dr Richard Hopkins, Managing Director ex-US markets said "*We are pleased with the outcome to this trial, which consolidates our strategic interests in the large market for chronic pain therapies."*

"In terms of next steps, these trial results are already informing the design of the trial we will be undertaking with Levin Growing targeting retired athletes with chronic pain. The data will also accelerate plans to expand Zelira's portfolio of chronic pain products, supported by clinical trial data, we will be launching into global markets and progressing into clinical development. These include an aged-care product that is on-track to launch in the US later this year and a larger chronic pain clinical trial we're planning for 2021."

"*We would like to acknowledge the dedicated teams at St Vincent's Hospital and Emerald Clinics and express our gratitude to the patients and supporting investigators/organisations who participated in the study*."

This announcement has been approved and authorised for release by the board of Zelira Therapeutics Limited.

Richard Hopkins
Managing Director

About Zelira Therapeutics (www.zeliratx.com)

Zelira Therapeutics Ltd is a leading global therapeutic medical cannabis company with access to the world's largest and fastest growing cannabis markets. Zelira owns a portfolio of proprietary revenue generating products and a pipeline of candidates undergoing clinical development that are positioned to enter global markets from 2020. The company is focused on developing branded cannabis products for the treatment of a variety of medical conditions.

The Company is undertaking product development programs targeting specific conditions (e.g. HOPE™) and human clinical trial programs focused on insomnia, autism and opioid reduction in patients with chronic non-cancer pain.

The Company conducts this work in partnership with world-leading researchers and organizations including Curtin University in Perth, Western Australia; the Telethon Kids Institute in Perth; the University of Western Australia, in Perth; St. Vincent's Hospital in Melbourne, Australia; and the Children's Hospital of Philadelphia (CHOP) in the United States.

The Company has developed two proprietary formulations (HOPE™) already launched and generating revenues in Pennsylvania, has laboratory capabilities to develop formulations in Pennsylvania and Louisiana with ability to conduct clinical trials and is establishing a national footprint across the US for the licensing of its products.

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