22 May 2025

Zelira Therapeutics Announces Full Study Publication of IRB Approved Observational Study Demonstrating Promising Efficacy and Safety of ZLT-L-007 Compared to Lyrica® (Pregabalin) in Diabetic Neuropathy

FULL STUDY PUBLICATION OF IRB APPROVED STUDY

Key Highlights

- Study demonstrates that ZLT-L-007 significantly outperforms Lyrica® (Pregabalin) in reducing pain intensity, improving sleep, and alleviating neuropathic symptoms.
- ZLT-L-007 monotherapy achieved an 85% reduction in daily pain scores by Day 90, compared to 30% with Lyrica®.
- Combination Therapy (ZLT-L-007 + Lyrica®) showed additive benefits, including complete resolution of pain-related sleep interference and affective pain scores.
- ZLT-L-007 achieved full resolution (100%) of specific debilitating pain types such as electric shock, stabbing, and burning pain.
- Participants reported substantial improvements in mood and quality of life, with depression scores decreasing by up to 61%.
- The study was conducted under an IRB-approved protocol and followed Good Clinical Practice (GCP) standards.
- No serious adverse events were reported; vital signs and laboratory safety markers remained stable across all treatment arms.
- These findings are based on a Phase I proof-of-concept study.

Zelira Therapeutics Ltd (ASX:ZLD, OTCQB:ZLDAF), a global leader in cannabinoid-based therapeutics, today announced the publication of its clinical study report titled "*Comparative Evaluation of ZLT-L-007, a Proprietary Cannabinoid-Based Therapy, and Pregabalin (Lyrica®) for Pain Reduction in Diabetic Neuropathy*." The study, now available for public and scientific review, marks a pivotal step forward in addressing diabetic peripheral neuropathy and highlights ZLT-L-007's potential to redefine standard-of-care treatment. See Fully Study report here.

Conducted as an IRB approved Comparative Observational, head-to-head trial, the study evaluated 60 adults diagnosed with diabetic neuropathy, randomised into three arms: Pregabalin (Lyrica®) monotherapy, ZLT-L-007 monotherapy, and Combination Therapy (ZLT-L-007 + Pregabalin). Over a 12-week period, patients were monitored across multiple domains of efficacy, safety, and tolerability. The results were compelling: ZLT-L-007 not only met the primary endpoint but also consistently outperformed Lyrica® across every major secondary endpoint without any serious adverse events reported.

Study Design and Methodology: Inclusion and Exclusion Criteria:

Participants enrolled in the study were adults aged between 18 and 85 years with a documented clinical diagnosis of diabetic neuropathy and a baseline Visual Analog Scale (VAS) pain score of 5 or greater. Additional inclusion criteria included enrollment in the Pennsylvania Medical Marijuana Program for eligible sites and the ability to comply with study procedures.

Key exclusion criteria included current substance or alcohol dependence, uncontrolled hypertension, significant psychiatric or cognitive disorders (such as dementia or psychosis), pregnancy or breastfeeding, and any concurrent cannabis use outside the study protocol. Subjects with any condition deemed by the investigator to compromise safety or the validity of the study were also excluded.

The trial was a 12-week, open-label, multi-arm Phase I observational study conducted under Institutional Review Board (IRB) approval and in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

A total of 75 patients were screened, and 60 were enrolled based on inclusion criteria including documented diabetic neuropathy, VAS pain score ≥5, and appropriate medical clearance. Participants were randomised in a 1:1:1 ratio into three groups:

- **Group 1:** Pregabalin monotherapy (initiated at 150 mg/day, titrated to 300 mg/day)
- **Group 2:** ZLT-L-007 monotherapy (oral proprietary cannabinoid formulation administered BID (twice daily) to QID (4 times daily) as tolerated)
- **Group 3:** Combination Therapy (concurrent administration of both above regimens)

The primary endpoint was the change in Daily Pain Numeric Rating Scale (NRS) scores from baseline to Days 30, 60, and 90. Secondary endpoints included changes in Visual Analog Scale (VAS), Sleep Interference (DSIS), Pain-Ten Domains, Neuropathic Pain Symptom Inventory (NPSI), Short Form McGill Pain Questionnaire (SF-MPQ), and Hospital Anxiety and Depression Scale (HADS). Safety was assessed through vital signs, liver and renal function tests, and adverse event reporting.

Key Study Findings by Endpoint:

1. Primary Endpoint — Daily Pain Numeric Rating Scale (NRS):

- ZLT-L-007 monotherapy achieved an **85% median reduction** in daily pain scores by Day 90.
- Combination Therapy achieved a **67% reduction**.
- Lyrica® (Pregabalin) monotherapy yielded a **30% reduction**.

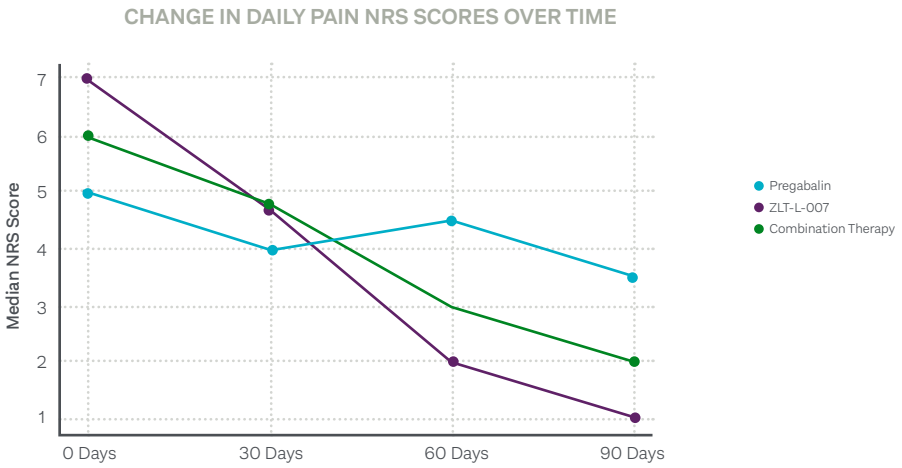

FIGURE 1. Change in Daily Pain NRS Scores Over Time.
Median Daily Pain Numeric Rating Scale (NRS) scores at baseline and Days 30, 60, and 90 by treatment group. ZLT-L-007 monotherapy and Combination Therapy achieved greater and more sustained pain reduction compared to Pregabalin monotherapy.

2. Visual Analog Scale (VAS):

- Both ZLT-L-007 and Combination Therapy achieved a **64% reduction** in pain intensity.
- Lyrica® achieved a **50% reduction** by Day 90.

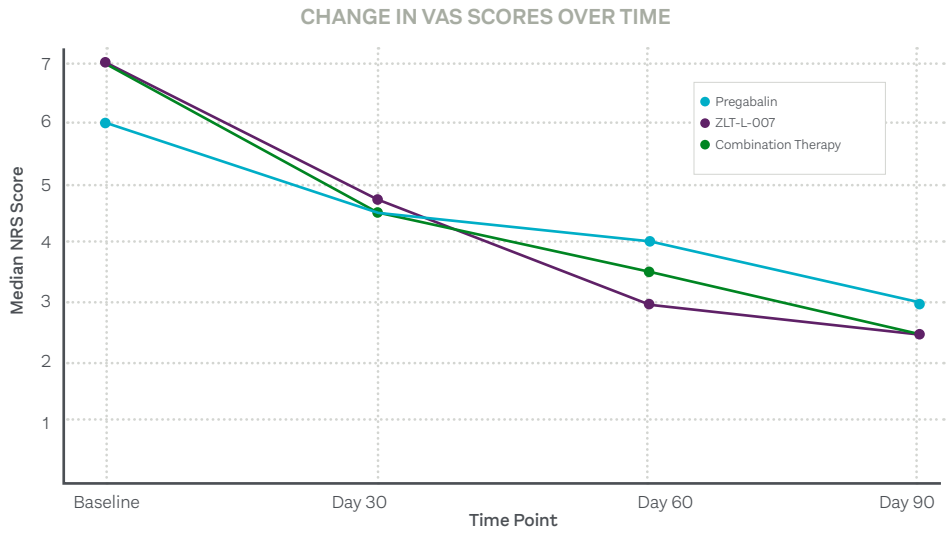

FIGURE 2. Change in VAS Scores Over Time Median
Visual Analog Scale (VAS) pain intensity scores at baseline and Days 30, 60, and 90 by treatment group. The ZLT-L-007 monotherapy and Combination Therapy groups demonstrated larger and more consistent reductions in pain intensity compared to Pregabalin.

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3. Symptom-Specific Pain (Pain-Ten Domains):

- ZLT-L-007 achieved **complete (100%) resolution** in electric shock, stabbing, and burning pain.
- Combination Therapy showed **≥90% reductions** in these domains.
- Lyrica® did not achieve full resolution in any of these specific symptom types.

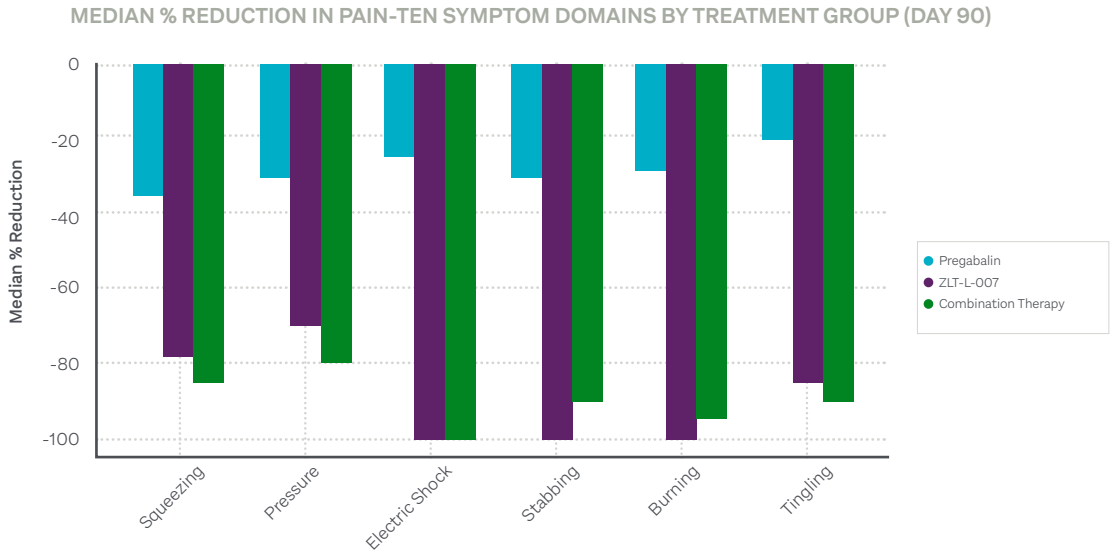

FIGURE 3: Median % reductions for each specific symptom domain
Median percentage reductions in symptom-specific pain severity at Day 90 for Pregabalin, ZLT-L-007, and Combination Therapy groups. ZLT-L-007 monotherapy achieved complete resolution (100% reduction) in electric shock, stabbing pain, and burning pain domains.

4. Sleep Quality — Daily Sleep Interference Scale (DSIS):

- Combination Therapy led to **complete resolution** of sleep interference by Day 90.
- ZLT-L-007 monotherapy achieved a **60% reduction**.
- Lyrica® achieved a **30% improvement**.

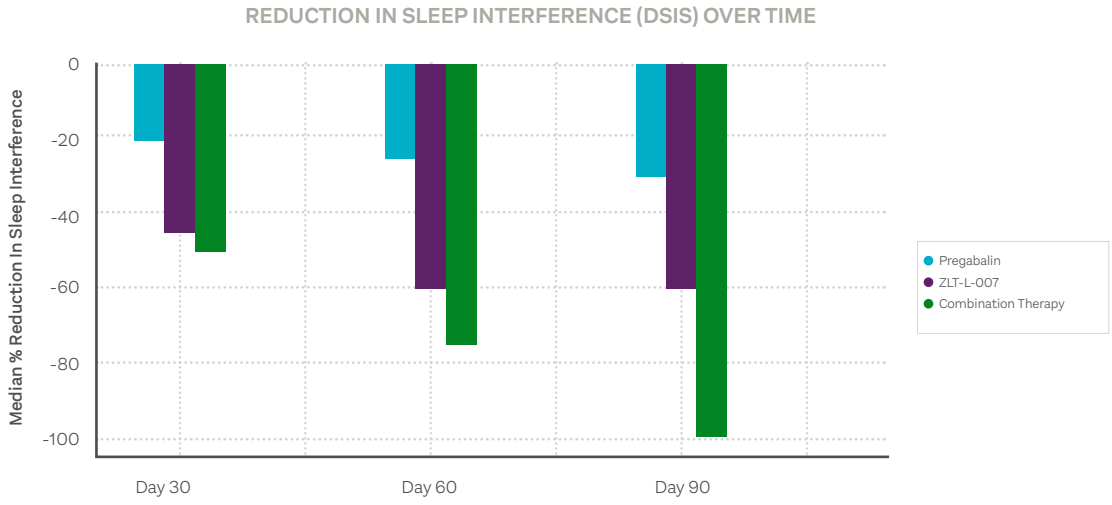

FIGURE 4. Reduction in Sleep Interference Over Time
Median percentage reductions in Daily Sleep Interference Scale (DSIS) scores at Days 30, 60, and 90 by treatment group. Combination Therapy achieved complete resolution of sleep interference by Day 90.

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5. Neuropathic Pain Symptom Inventory (NPSI):

- Combination Therapy reduced total NPSI scores by **53.1%**.
- ZLT-L-007 monotherapy: **30% reduction**.
- Lyrica® monotherapy: **25.7% reduction**.

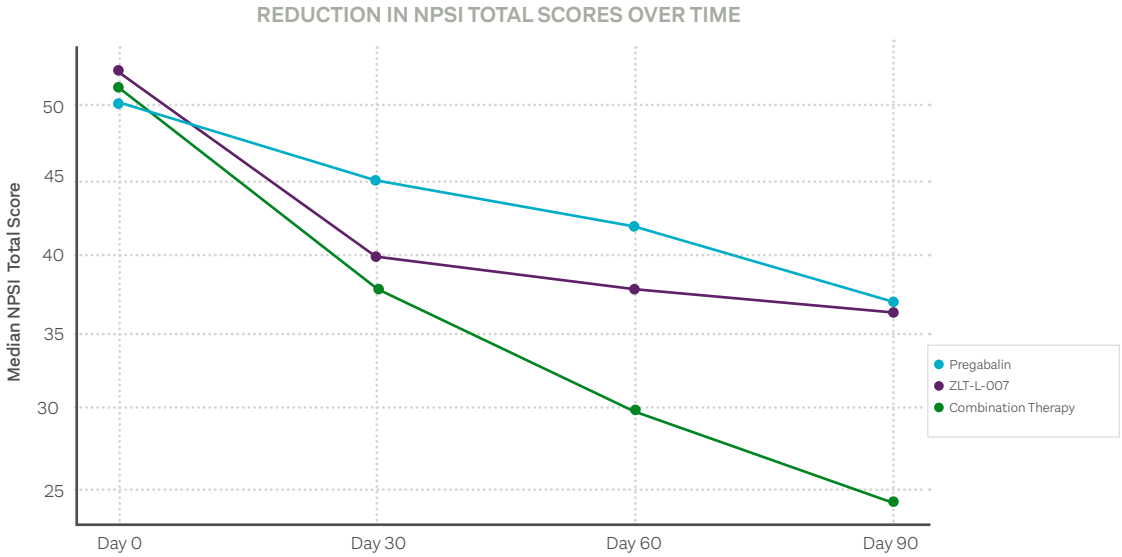

FIGURE 5. Reduction in NPSI Total Scores Over Time
Median total Neuropathic Pain Symptom Inventory (NPSI) scores at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy demonstrated the most pronounced reduction in neuropathic pain burden by Day 90.

6. Short Form McGill Pain Questionnaire (SF-MPQ):

- Combination Therapy: **73% reduction in sensory scor**es and **100% resolution of affective pain**.
- ZLT-L-007: **54% sensory** and **90% affective score** reductions.
- Lyrica®: **33% sensory** and **50% affective score** reductions.

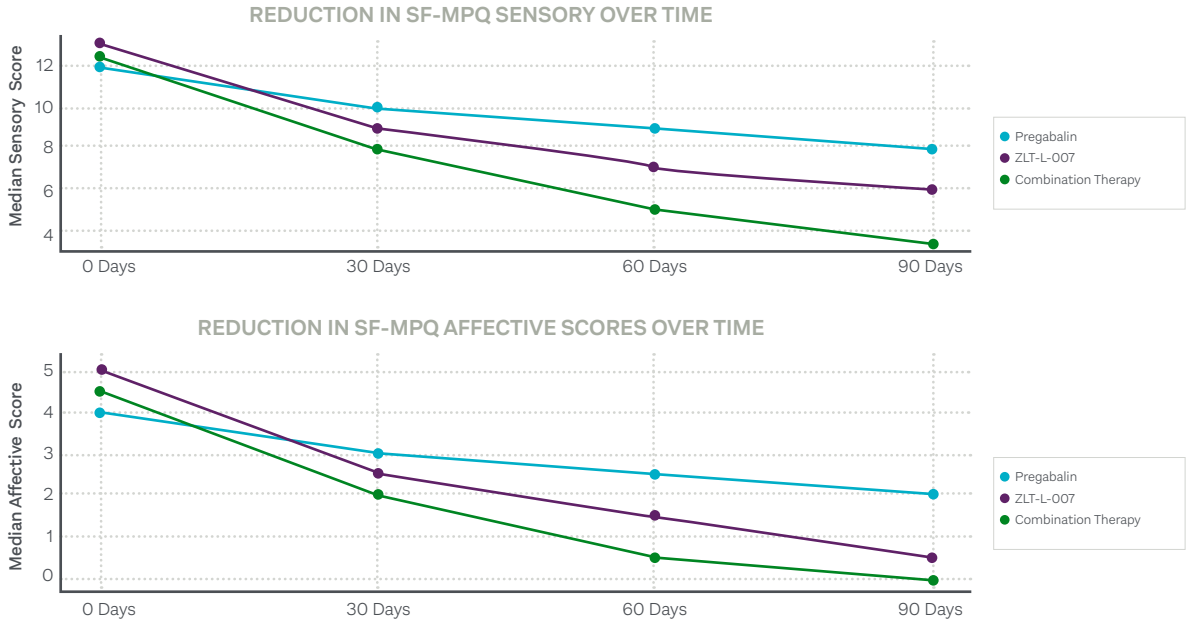

FIGURE 6. Reduction in SF-MPQ Sensory and Affective Scores Over Time
Median sensory and affective scores from the Short Form McGill Pain Questionnaire (SF-MPQ) at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy achieved the largest reductions, including complete resolution of affective pain scores by Day 90.

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7. Psychological Health — Hospital Anxiety and Depression Scale (HADS):

- Depression scores dropped by **61%** with Combination Therapy, **41%** with ZLT-L-007, and **26%** with Lyrica®.
- Anxiety scores remained stable in the Lyrica® group but improved slightly in ZLT-L-007 and Combination arms.

FIGURE 7. Changes in HADS Anxiety and Depression Scores Over Time
Median HADS Anxiety (HADS-A) and HADS Depression (HADS-D) scores at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy achieved the greatest reduction in depression scores by Day 90.

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8. Safety Profile:

The safety and tolerability of the study treatments were evaluated by monitoring:

- Vital signs: Pulse rate, blood pressure (systolic/diastolic), and respiratory rate.
- Clinical laboratory biomarkers: Liver enzymes (AST, ALT), renal function markers (creatinine, BUN), and serum electrolytes (sodium, potassium, chloride).

Safety evaluations were performed at baseline and at regular intervals (Days 30, 60, and 90) throughout the 12-week treatment period.

- **Vital signs** and **laboratory markers** (liver enzymes, renal function, electrolytes) remained stable.
- **No serious adverse events** or treatment-related discontinuations occurred. Overall, ZLT-L-007, whether administered alone or alongside Pregabalin, was well tolerated. No new or unexpected safety signals were identified during the 12-week study period, and no participants discontinued treatment due to adverse events.

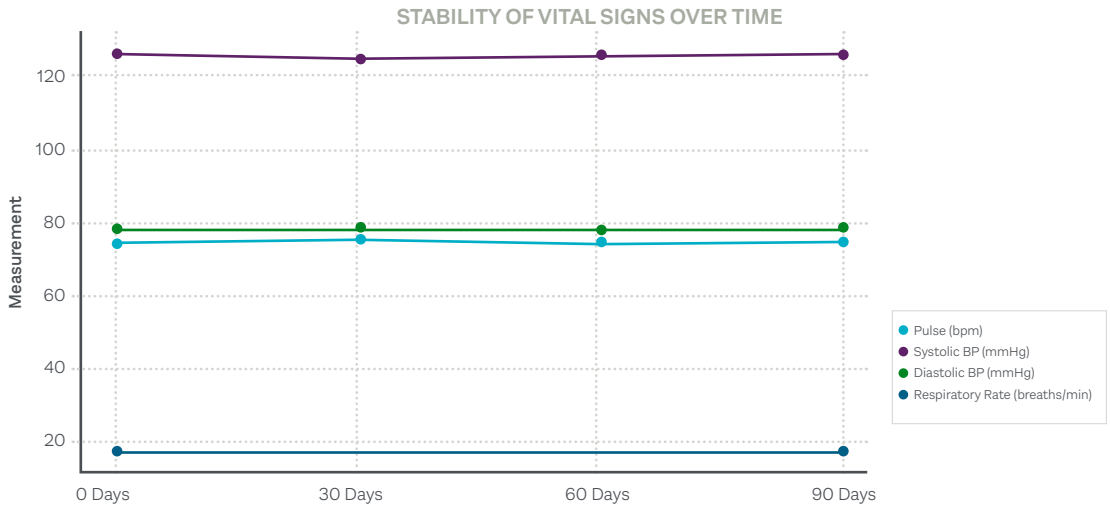

FIGURE 8. Stability of Vital Signs Over Time
Mean vital signs (pulse, blood pressure, and respiratory rate) remained stable across all treatment groups over the 90-day study period.

MEAN VITAL SIGNS ACROSS STUDY TIMEPOINTS

VITAL SIGN	TIME POINT	PREGABALIN GROUP	ZLT-L-007 GROUP	COMBINATION GROUP
Pulse (bpm)	Baseline	74.0	75.5	74.5
Pulse (bpm)	Day 30	75.0	74.8	74.7
Pulse (bpm)	Day 60	74.2	75.0	74.4
Pulse (bpm)	Day 90	74.5	74.7	74.2
Systolic BP (mmHg)	Baseline	126.0	128.0	127.5
Systolic BP (mmHg)	Day 30	125.0	127.5	126.0
Systolic BP (mmHg)	Day 60	125.5	127.0	126.5
Systolic BP (mmHg)	Day 90	126.0	127.2	126.0
Diastolic BP (mmHg)	Baseline	78.0	79.0	78.5
Diastolic BP (mmHg)	Day 30	78.5	78.0	78.0
Diastolic BP (mmHg)	Day 60	78.0	78.5	77.5
Diastolic BP (mmHg)	Day 90	78.2	78.0	77.8
Respiratory Rate (breaths/min)	Baseline	16.0	16.5	16.2
Respiratory Rate (breaths/min)	Day 30	16.2	16.0	16.0
Respiratory Rate (breaths/min)	Day 60	16.0	16.3	16.0
Respiratory Rate (breaths/min)	Day 90	16.0	16.2	16.0

The results of this POC study demonstrates ZLT-L-007 as a highly promising cannabinoid-based therapy that not only relieves pain more effectively than Lyrica® but also addresses symptom complexity, sleep disturbance, emotional burden, and overall quality of life.

While Lyrica® has been widely used as a first-line treatment for diabetic neuropathic pain, some patients may experience limited benefits due to variable response and side effects such as dizziness, drowsiness, and cognitive challenges. The encouraging performance of ZLT-L-007 across multiple study endpoints—including notable improvement in pain symptoms and sleep quality—suggests its potential as a meaningful alternative or complement to existing therapies.

Equally important is the fact that ZLT-L-007 achieved these outcomes with a clean safety profile and no reported serious adverse events—a critical consideration in chronic conditions where long-term tolerability is essential.

As a Phase I proof-of-concept study conducted under an IRB-approved observational protocol, these findings, while highly encouraging, was designed to generate early clinical signals. As such, the results are preliminary in nature and require validation through larger, randomised and controlled trials to fully establish the therapeutic potential of ZLT-L-007. Zelira is committed to building upon this strong foundation through larger, randomised, double-blind, placebo-controlled trials to validate these outcomes.

This study provides an early but powerful signal that ZLT-L-007 may represent a new paradigm in the treatment of diabetic neuropathy—one that is safer, broader-acting, and more effective than existing therapies.

Quote from Dr. Oludare Odumosu:

This study is a turning point not just for Zelira, but for the millions of patients living with the daily burden of diabetic neuropathy. The results reinforce what we've always believed—ZLT-L-007 is more than a product, it's a platform for transformational change in how we approach and manage chronic pain conditions globally. As a company committed to advancing science with purpose, we are incredibly energised by both the clinical promise and the broad therapeutic potential this data represents. This successful proof-of-concept study validates our product development model and underscores our ability to generate meaningful clinical outcomes within a regulated pharmaceutical framework. It strengthens our long-term value proposition to investors and highlights the scalability of our cannabinoid-based drug development pipeline. For our strategic partners, it is a compelling demonstration of Zelira's execution capabilities, clinical discipline, and commercial readiness. We are just getting started.

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

For further information please contact

Company
Dr Oludare Odumosu
Managing Director & CEO
+1 909 855 0675
oodumosu@zeliratx.com

Investors
Rebecca Culbertson
Executive Director, Automic Group
+61 400 955 295
rebecca.culbertson@automicgroup.com.au

Australia
Level 3, 101 St Georges Terrace
Perth WA 6000, AUSTRALIA
+61 8 6558 0886
Fax: +61 8 6316 3337
enquiries@zeliratx.com
www.zeliratx.com
ACN 103 782 378

USA
5110 Campus Drive, Suite 150
Plymouth Meeting, PA 19462
United States Of America
+1 484 630 0650

Zelira Therapeutics Ltd (ASX:ZLD, OTCQB:ZLDAF) Zelira is a leading global biopharmaceutical company in the research, development and commercialisation of clinically validated cannabinoid-based medicines. Zelira owns a portfolio of proprietary revenue generating products and a pipeline of candidates undergoing clinical development positioned to enter global markets. The Company is focused on developing and clinically validating branded cannabinoid-based medicines in its prescription [Rx] business for the treatment of a variety of medical conditions including insomnia, autism and chronic noncancer pain as well as offering over the counter [OTC] products.

Zelira has established a special purpose vehicle (SPV) to conduct FDA Phase 1, Phase 2 and Phase 3 clinical trials for Zelira's proprietary and patent protected HOPE® 1. Zelira has contributed to the SPV its HOPE® 1 product, IP and real-world data for 55% equity ownership of the SPV. Cash investors will contribute a total of circa US$35 million to fund the SPV and US FDA trials for HOPE® 1 in exchange for a cumulative equity interest of 45% of the SPV. Zelira will manage the SPV as part of its business platform. The SPV has appointed iNGENū CRO Pty Ltd (iNGENū) as its Contract Research Organisation (CRO) to lead the clinical validation and regulatory registration of the study product with the US FDA through the submission of an Investigative New Drug (IND) application.

In May 2023, Zelira completed an IRB approved strategically designed multi-arm, head-to-head study targeting diabetic nerve pain. The clinical trial included a comprehensive comparison against the widely recognised and highly successful multi-billion dollar revenue generating drug Lyrica® (Pregabalin). With the findings underscoring the exceptional efficacy of our treatments in managing pain, with ZLT-L-007 demonstrating the most substantial reduction in pain severity, particularly at the 60-day and 90-day follow-up periods. Zelira has developed Enhanced Distillate Capture and Dissolution Matrix (EDCDM) technology under the brand name Zyraydi™, that solves the problem of non-uniformity and separation of cannabinoid from powder bed, opening new ways to develop pharmaceutical grade solid oral dosage forms such as capsules and tablets. Zelira will be assessing opportunities for commercialisation of this technology.

Zelira's Rx business generates revenue from its proprietary medication, HOPE. The Company has two proprietary formulations under the HOPE® brand that are generating revenue in Australia, Washington, D.C., Pennsylvania and Louisiana. Zelira will also be expanding commercialisation of ZENIVOL® – the world's first clinically validated cannabinoid drug for treatment of chronic insomnia into Germany via its German commercialisation partner Adjupharm GmbH following recent approval from German regulatory authority BfArM. Zelira's OTC products in the oral and dermatology health care sectors are also generating revenue. Zelira, in partnership with SprinJeneCBD, launched a full line of oral care products, currently generating revenue in the US. Zelira also launched in 2021 the RAF FIVE™ brand, which consists of five OTC acne treatment products using a proprietary formulation incorporating cannabidiol (CBD).

For further information, please visit: **zeliratx.com**