Comparative Evaluation of ZLT-L-007, and Pregabalin (Lyrica®) for Pain Reduction in Diabetic Neuropathy: A Phase I Proof of Concept (POC) Observational Study

IRB-approved, observational, multi-arm, head-to-head Phase I study to evaluate the clinical efficacy, safety, and tolerability of ZLT-L-007, a proprietary cannabinoid-based formulation, compared to Pregabalin in subjects with diabetic neuropathy

Study Report

Zelira Therapeutics LTD

Level 3, 101 St Georges Terrace, Perth, WA 6000, Australia.

5110 Campus Dr Ste 150 Plymouth Meeting, PA, 19462

Abstract

Background: Diabetic neuropathy represents a significant burden for individuals living with diabetes, with neuropathic pain being a predominant and debilitating symptom. Standard treatments, including pregabalin (Lyrica®), are limited by moderate efficacy and significant adverse events.

Objective: To evaluate the clinical efficacy, safety, and tolerability of ZLT-L-007, a proprietary cannabinoid-based formulation, compared to pregabalin in subjects with diabetic neuropathy.

Methods: This IRB-approved, observational, multi-arm, head-to-head Phase I study enrolled 60 adults diagnosed with diabetic neuropathy. Subjects were randomized into three groups: pregabalin only, ZLT-L-007 only, or a combination of both. The primary endpoint was *change from baseline* in Daily Pain Numeric Rating Scale (NRS). Secondary endpoints included Visual Analog Scale (VAS), Short Form McGill Pain Questionnaire (SF-MPQ), Daily Sleep Interference Scale (DSIS), and psychological wellbeing assessments.

Results: ZLT-L-007 demonstrated significant reductions in pain scores compared to pregabalin alone, achieving the primary and multiple secondary endpoints without any Serious Adverse Events (SAEs).

Conclusion: ZLT-L-007 offers a promising therapy for diabetic neuropathy, with superior efficacy and an excellent safety profile relative to pregabalin (Lyrica®), supporting further clinical development.

Introduction

Diabetic neuropathy is one of the most common complications of diabetes mellitus, affecting approximately 50% of diabetic patients over the course of their illness. It encompasses a range of nerve disorders caused by diabetes, most notably *distal symmetric peripheral neuropathy*, which primarily impacts the feet and legs, and subsequently, the hands and arms.

The pathogenesis of diabetic neuropathy is complex and multifactorial, involving chronic hyperglycemia-induced metabolic and vascular insults that culminate in nerve ischemia and demyelination. Clinical manifestations include pain, burning sensations, tingling, numbness, heightened sensitivity to touch, and muscle weakness, leading to significant impairments in mobility, sleep, and emotional wellbeing.

First-line pharmacological agents such as pregabalin and gabapentin are commonly prescribed for neuropathic pain. However, their efficacy remains modest, and they are frequently associated with undesirable side effects, including dizziness, weight gain, somnolence, peripheral edema, and cognitive disturbances. Opioid analgesics, although effective for acute pain, are generally discouraged from chronic neuropathic pain due to the risk of tolerance, dependence, and addiction.

Given these limitations, there is an urgent and unmet need for safer, more effective, and better-tolerated therapies for diabetic neuropathic pain. Cannabinoid-based therapeutics have emerged as promising alternatives, supported by preclinical and early clinical studies suggesting analgesic, anti-inflammatory, neuroprotective, and anxiolytic effects.

ZLT-L-007 is a proprietary cannabinoid-based formulation developed by Zelira Therapeutics, combining high-purity CBD, CBG, Δ8-THC, and specific terpenes (myrcene and linalool) optimized for neuropathic pain management. This study aimed to evaluate ZLT-L-007 in direct comparison to pregabalin (Lyrica®), leveraging a head-to-head clinical design powered to detect statistical significance.

Pharmaceutical Approaches to Treating Diabetic Neuropathy

Background and Current Standard of Care

Diabetic neuropathy, particularly painful distal symmetric polyneuropathy, remains a formidable clinical challenge due to its chronicity, impact on quality of life, and limited therapeutic options. The primary goal of treatment is symptomatic management: alleviating pain, improving functional status, and preventing further neurological decline.

Current pharmacologic and non-pharmacologic treatments include:

- **Anti-seizure medications**: Gabapentin and pregabalin are widely used to modulate aberrant neuronal excitability and reduce neuropathic pain.
- **Antidepressants**: Tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) offer relief for mild to moderate symptoms by modulating central pain pathways.
- **Topical therapies**: Creams such as capsaicin provide localized symptomatic relief.
- **Complementary therapies**: Transcutaneous electrical nerve stimulation (TENS), hypnosis, relaxation training, biofeedback, acupuncture, and specialized orthopedic shoes may provide adjunctive benefits.

Despite these interventions, many patients experience incomplete relief or discontinue therapy due to adverse effects, highlighting the unmet need for novel and better-tolerated therapeutic options.

Cannabinoids as Emerging Therapies in Neuropathic Pain

Cannabis, known to humanity for millennia, has been rediscovered in modern medicine following regulatory liberalization in several jurisdictions. Two principal bioactive cannabinoids have been identified: the psychoactive Δ9-tetrahydrocannabinol (Δ9-THC) and the non-psychoactive cannabidiol (CBD). Cannabidiol (CBD) and cannabigerol (CBG), two non-psychoactive cannabinoids, have demonstrated the ability to modulate multiple pain-related pathways, including serotonin receptors (5-HT1A), adenosine reuptake inhibition, transient receptor potential vanilloid 1 (TRPV1) modulation, and endocannabinoid system interactions. Moreover, delta-8-tetrahydrocannabinol (Δ8-THC), a minor cannabinoid, is thought to exert analgesic effects with less psychotropic impact compared to its more prominent isomer, Δ9-THC.

Cannabinoid receptors, primarily CB1 (central nervous system) and CB2 (immune system), mediate the effects of endocannabinoids and Phyto cannabinoids. While Δ9-THC acts as a partial agonist at both receptors, producing psychoactive effects, CBD exhibits a complex pharmacology, modulating receptor activity without directly inducing psychotropic outcomes.

Studies have demonstrated that CBD acts as a negative allosteric modulator of the CB1 receptor, reducing the receptor's affinity for Δ9-THC and thus mitigating psychotropic effects. Moreover, CBD interacts with a broad range of molecular targets, including:

- **5-HT1A receptors**: Enhancing serotonergic neurotransmission, leading to anxiolytic and antidepressant effects.
- **TRPV1, TRPV2, TRPM8, and TRPA1 channels**: Modulating pain and inflammatory pathways.
- **GPR55 inhibition**: Contributing to anti-inflammatory activity.
- **Equilibrative nucleoside transporters (ENTs)**: Increasing adenosine signaling and thereby providing neuroprotection.

CBD's polyphenolic structure also renders it a potent antioxidant, which may protect against oxidative stress-induced neuronal injury. CBD has been shown to enhance the therapeutic window of Δ9-THC by reducing its psychoactivity. This synergy is exemplified in botanical drug formulations such as Nabiximols (Sativex®), which combine equal parts of Δ9-THC and CBD for superior efficacy in spasticity and pain syndromes.

Pharmacokinetically, CBD is extensively metabolized by hepatic enzymes (CYP3A4 and CYP2C9/19), with a terminal half-life ranging from 18 to 32 hours. It is excreted predominantly via feces, with minimal urinary elimination.

Clinical Evidence Supporting Cannabinoids for Chronic Pain

A landmark systematic review by the American National Academies of Sciences, Engineering, and Medicine concluded there is substantial evidence that cannabis is effective for the treatment of chronic pain in adults. Nevertheless, heterogeneity in cannabinoid composition, dosing, and delivery methods across studies necessitates further well-controlled clinical trials to define optimal therapeutic regimens. Multiple cannabinoid-based therapies are currently at various stages of clinical development and commercialization, addressing indications ranging from epilepsy to spasticity to chronic pain (Table 1).

Table 1: Selected Cannabinoid-Based Therapeutics in Development and Commercialization

Drug Name	Composition	Indication	Status	Notes
Epidiolex®	Pure CBD	Lennox-Gastaut and Dravet Syndromes	Approved (FDA)	First FDA-approved CBD drug
Sativex® (Nabiximols)	1:1 Δ9-THC:CBD	Spasticity in MS	Approved (EU, Canada)	Improves tolerability over Δ9-THC alone
Dronabinol	Synthetic Δ9-THC	Chemotherapy-induced nausea	Approved (FDA)	Limited by psychotropic effects
Nabilone	Synthetic cannabinoid	CINV, Neuropathic pain	Approved (FDA)	Psychoactive

Abbreviations: MS = Multiple Sclerosis; CINV = Chemotherapy-Induced Nausea and Vomiting.

Delta-8-Tetrahydrocannabinol (Δ8-THC): A Promising Cannabinoid for Pain Management

Delta-8-tetrahydrocannabinol (Δ8-THC) is a minor, naturally occurring cannabinoid in the cannabis plant that has recently attracted significant scientific and therapeutic interest due to its distinctive pharmacological profile. Although Δ8-THC is structurally analogous to Δ9-THC, the primary psychoactive constituent of cannabis, a slight variation in the position of a carbon-carbon double bond between the two molecules yields important differences in their pharmacodynamics [1-3].

Δ8-THC binds to the CB1 receptor in the central nervous system, similarly to Δ9-THC, but with approximately 20–30% lower affinity [2]. This results in a milder psychoactive profile, reducing the risk of anxiety, dysphoria, and cognitive disruption often associated with Δ9-THC [1-3]. Critically, Δ8-THC retains potent analgesic, anti-inflammatory, antiemetic, and anxiolytic effects, aligning with therapeutic goals in neuropathic pain management [1-3].

Furthermore, Δ8-THC exhibits greater molecular stability than Δ9-THC, being less prone to oxidation and degradation, which supports more consistent pharmacological effects and extended shelf life in pharmaceutical formulations [2,4]. This enhanced chemical stability reduces variability and increases the reliability of dosing — critical parameters in the development of cannabinoid-based therapeutics.

From a therapeutic perspective, Δ8-THC offers a unique profile:

- **Preservation of analgesic efficacy** via partial CB1 receptor agonism.
- **Significant reduction in psychotropic intensity**, improving safety and tolerability in vulnerable populations.
- **Enhanced chemical stability**, promoting better product shelf-life and dosing consistency.

Thus, the incorporation of Δ8-THC into the ZLT-L-007 formulation reflects a strategic scientific choice: to capture the well-documented benefits of CB1-mediated analgesia while mitigating the psychoactivity and instability that often limit Δ9-THC-based therapeutics.

While large-scale randomized controlled trials (RCTs) evaluating Δ8-THC remain ongoing, preclinical studies and mechanistic analyses collectively indicate a strong therapeutic rationale for utilizing Δ8-THC over Δ9-THC in the management of diabetic neuropathy and other chronic pain states [1-4].

ZLT-L-007's deliberate inclusion of Δ8-THC thus represents an evidence-based innovation, aimed at maximizing efficacy, improving tolerability, and delivering superior outcomes in chronic neuropathic pain syndromes.

Methods

Study Design

This was a Phase I, open-label, observational, multi-arm, IRB-approved study designed to compare the clinical efficacy, safety, and tolerability of ZLT-L-007, a proprietary cannabinoid formulation, to pregabalin (Lyrica® 300 mg/day) for the treatment of diabetic neuropathy-associated pain.

The study was conducted in accordance with Good Clinical Practice (GCP) guidelines and the ethical principles outlined in the Declaration of Helsinki. All study procedures, including the protocol and informed consent documents, were reviewed and approved by Institutional Review Boards (IRBs) prior to initiation, ensuring ethical oversight and participant protection throughout the study period. (*see full protocol for details*).

Objective

The primary objective of the study was to directly compare the clinical performance of Zelira's patent-protected ZLT-L-007 against pregabalin (Lyrica®) with respect to:

- Efficacy in reducing pain associated with diabetic neuropathy.
- Safety and tolerability profiles over the 12-week observation period.

Participants

Eligibility Criteria

Subjects were eligible for enrollment if they met all of the following inclusion criteria:

- Adults aged between 18 and 85 years.
- Documented clinical diagnosis of diabetic neuropathy.
- Baseline Visual Analog Scale (VAS) pain score of ≥5.
- Enrollment in the Pennsylvania Medical Marijuana Program (for applicable sites).

Exclusion Criteria

Key exclusion criteria included:

- Current substance or alcohol dependence.
- Diagnosis of dementia, psychosis, or presence of uncontrolled hypertension.
- Concurrent cannabis use outside the study protocol.
- Pregnancy or breastfeeding at the time of screening.
- Other medical or psychiatric conditions deemed by the Investigator to compromise study participation (*see full protocol for details*).

Treatment Arms

Table 2: Subjects were randomized into one of three treatment groups:

Group	Treatment	Dosing Regimen
1	Pregabalin only	150 mg/day for 1 week, escalated to 300 mg/day thereafter
2	ZLT-L-007 only	75 mg cannabinoids twice daily (BID); dose escalation to three or four times daily (TID/QID) permitted based on clinical response
3	Combination Therapy (Pregabalin + ZLT-L-007)	Concurrent administration of pregabalin and ZLT-L-007 as above

Investigational Product Details: ZLT-L-007

ZLT-L-007 is a proprietary, orally administered cannabinoid-based formulation specifically developed for the management of neuropathic pain. It comprises a standardized combination of pharmacologically active cannabinoids chosen for their complementary mechanisms of action, including modulation of nociceptive signaling, inflammatory cascades, and neuroprotective pathways. The formulation is further enhanced with select botanical terpenes intended to support systemic absorption and augment therapeutic potential. As a proprietary blend, the exact composition is confidential, and the product is manufactured under stringent quality assurance protocols to ensure consistency, stability,

and clinical performance. Capsules were manufactured under Good Manufacturing Practice (GMP) conditions and dispensed to patients for self-administration at home, following strict accountability procedures (*see full protocol for details*).

Study Flow Diagram

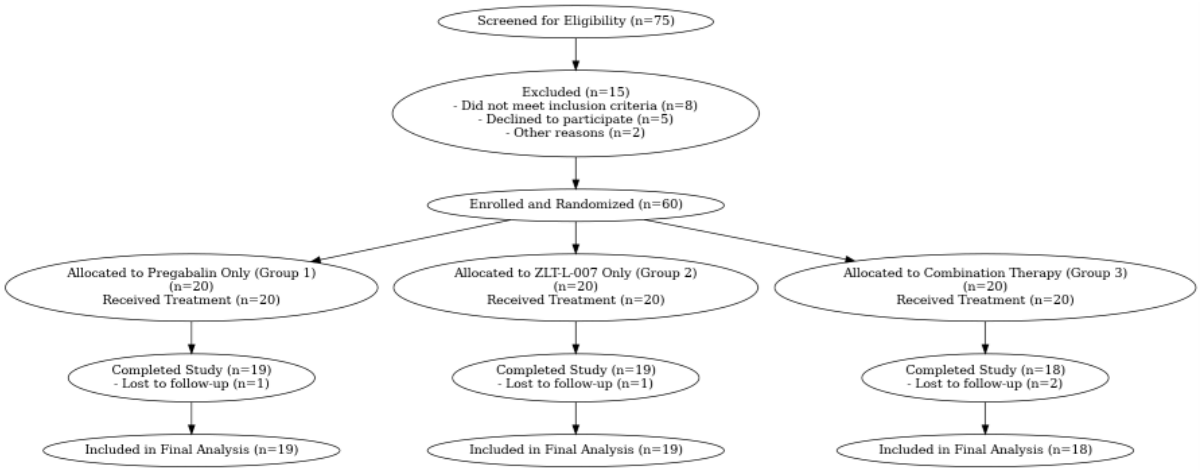


Figure 1. **Study flow diagram showing screening, enrollment, allocation, follow-up, and inclusion in the final analysis.**

Endpoints

Primary Endpoint

- Change in Daily Pain Numeric Rating Scale (NRS) scores from baseline to Days 30, 60, and 90.

Secondary Endpoints

- Change in Visual Analog Scale (VAS) pain intensity scores.
- Change in Short Form McGill Pain Questionnaire (SF-MPQ) scores.
- Sleep quality assessed via the Daily Sleep Interference Scale (DSIS).
- Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC).
- Psychological status assessed via the Hospital Anxiety and Depression Scale (HADS).
- Safety evaluations based on adverse event (AE) reporting, vital signs, and clinical laboratory assessments.

Full definitions of all efficacy and safety endpoints, as well as criteria for treatment-emergent adverse events (TEAEs), are provided in the full protocol (*see full protocol for details*).

Statistical Analysis

Given the exploratory nature of this Phase I observational study, statistical analyses were primarily descriptive:

- Continuous variables were summarized using **means**, **standard deviations**, **medians**, **ranges**, and **95% confidence intervals**.
- Categorical variables were summarized using **counts** and **percentages**.
- No imputation was performed for missing data.
- The study was powered to detect clinically meaningful differences between treatment arms but was not formally designed for inferential hypothesis testing at a pre-specified alpha level

Table 3: Statistical Analysis Plan (SAP) Summary

Category	Description
Study Design	Phase I, open-label, observational, multi-arm comparative study.
Analysis Populations	Full Analysis Set (FAS): All subjects who received at least one dose of investigational product.
Primary Endpoint	Change in Daily Pain Numeric Rating Scale (NRS) from baseline to Days 30, 60, and 90.
Secondary Endpoints	Change in VAS, SF-MPQ, DSIS, CGIC, PGIC, HADS scores; Safety assessments (AEs, vitals, labs).
Descriptive Statistics	Means, medians, standard deviations, ranges, and 95% confidence intervals.
Handling of Missing Data	No imputation. Missing data reported as observed.
Safety Analysis	All subjects who received at least one dose evaluated for adverse events, serious adverse events, and discontinuations.
Software	Statistical analyses performed using validated statistical software (e.g., SAS v9.4 or R 4.2.1).
Hypothesis Testing	No formal inferential testing; exploratory statistical comparisons where appropriate.
Protocol Deviations	All major protocol deviations were listed and described; subjects with major deviations remained included in FAS analysis.

Results:

Participant Disposition

A total of 75 participants were screened for eligibility, out of which 60 participants met the inclusion criteria and were randomized in a 1:1:1 ratio into three treatment groups:
- Group 1: Pregabalin monotherapy (n=20)
- Group 2: ZLT-L-007 monotherapy (n=20)
- Group 3: Combination Therapy (Pregabalin + ZLT-L-007) (n=20)

All randomized participants received at least one dose of the assigned intervention and were included in the Full Analysis Set (FAS). A total of 56 participants (93.3%) completed the 12-week study, with four participants (6.7%) lost to follow-up.

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics were comparable across the three treatment groups, demonstrating successful randomization. The mean (SD) age of participants ranged from 56.5 years in the ZLT-L-007 group to 61.3 years in the Pregabalin group. Females represented approximately 48.3% of the overall study population. The majority of participants were White (72.7% to 94.4%) and Non-Hispanic (>95%) across all treatment groups. Mean Body Mass Index (BMI) was 33.77 kg/m^2, indicating a predominantly overweight to obese study population. Other baseline characteristics, including mean height and weight, were similarly balanced between groups.

Table 4. A summary of key baseline demographic and clinical variables

Characteristic	Pregabalin (n=20)	ZLT-L-007 (n=20)	Combination (n=20)	Total (N=60)
Mean Age (years)	61.3	56.5	58.2	58.6
Female, n (%)	8 (40%)	10 (50%)	11 (55%)	29 (48.3%)
White, n (%)	17 (85%)	18 (90%)	19 (95%)	54 (90%)
Non-Hispanic, n (%)	19 (95%)	18 (90%)	20 (100%)	57 (95%)
Mean BMI (kg/m^2)	34.0	33.5	33.8	33.77
Mean Weight (kg)	220.0	221.5	220.8	220.76
Mean Height (cm)	168.0	167.5	168.2	167.9

Note: Data are presented as mean values unless otherwise indicated.

Primary Endpoint: Daily Pain Numeric Rating Scale (NRS)

The primary efficacy outcome was the change from baseline in the Daily Pain Numeric Rating Scale (NRS) score, evaluated at Days 30, 60, and 90.

At baseline:
- Median NRS scores were 5.0 in the Pregabalin group, 7.0 in the ZLT-L-007 group, and 6.0 in the Combination group.

Across the study duration:
- All three groups exhibited a reduction in NRS scores, indicating improvement in pain severity.
- However, the magnitude and consistency of improvement differed notably between groups.

By Day 90:
- Pregabalin group: Median NRS decreased to 3.5, representing a 30% reduction from baseline.
- ZLT-L-007 group: Median NRS decreased substantially to 1.0, equating to an ~85% reduction.
- Combination group: Median NRS decreased to 2.0, representing a ~67% reduction.

The ZLT-L-007 monotherapy group demonstrated the greatest and most consistent reduction in daily pain scores over the 12-week period. Combination therapy also achieved significantly better outcomes than Pregabalin monotherapy.

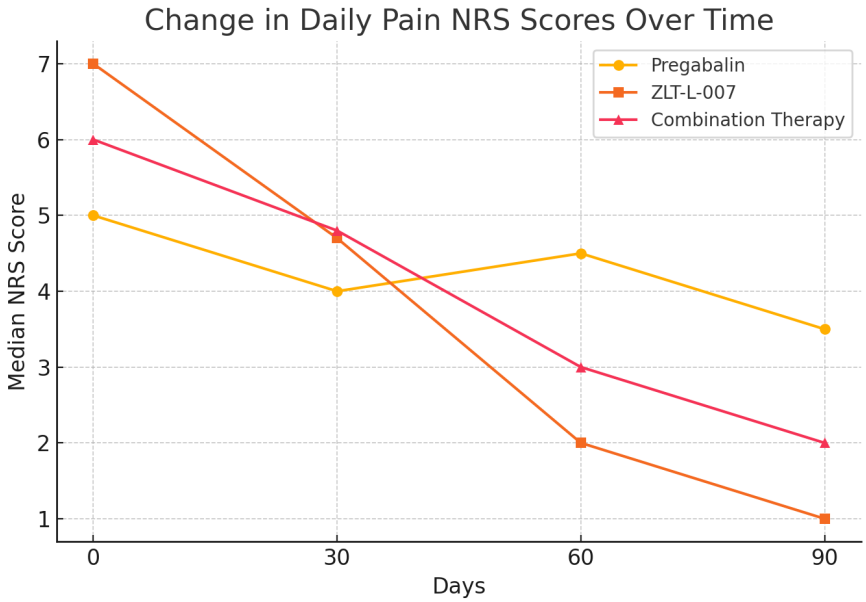


Figure 2. Change in Daily Pain NRS Scores Over Time
Median Daily Pain Numeric Rating Scale (NRS) scores at baseline and Days 30, 60, and 90 by treatment group. ZLT-L-007 monotherapy and Combination Therapy achieved greater and more sustained pain reduction compared to Pregabalin monotherapy.

Table 5. Median Daily Pain NRS Scores and Percentage Change Over Time

Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
Baseline	5.0	7.0	6.0
Day 30	4.0 (-20%)	4.7 (-33%)	4.8 (-20%)
Day 60	4.5 (-10%)	2.0 (-71%)	3.0 (-50%)
Day 90	3.5 (-30%)	1.0 (-85%)	2.0 (-67%)

Note: Values are median NRS scores at each timepoint. Values in parentheses represent % change from baseline.

Secondary Endpoints

Visual Analog Scale (VAS)

The Visual Analog Scale (VAS) was used as a secondary endpoint to measure the intensity of neuropathic pain experienced by participants across the three treatment groups. VAS is a validated tool where patients rate their pain on a scale from 0 (no pain) to 10 (worst possible pain).

VAS Scores Over Time

At baseline:
- Pregabalin group: Median VAS score was 6.0.
- ZLT-L-007 group: Median VAS score was 7.0.
- Combination group: Median VAS score was 7.0.

By Day 90:
- Pregabalin group: VAS scores improved to 3.0, indicating a 50% reduction from baseline.
- ZLT-L-007 group: VAS scores decreased to 2.5, representing a 64% reduction.
- Combination group: VAS scores also declined to 2.5, corresponding to a 64% reduction.

Across the 12-week study period, both ZLT-L-007 and Combination therapies consistently outperformed Pregabalin monotherapy in reducing pain intensity. Improvement was evident as early as Day 30 and was sustained through Day 90.

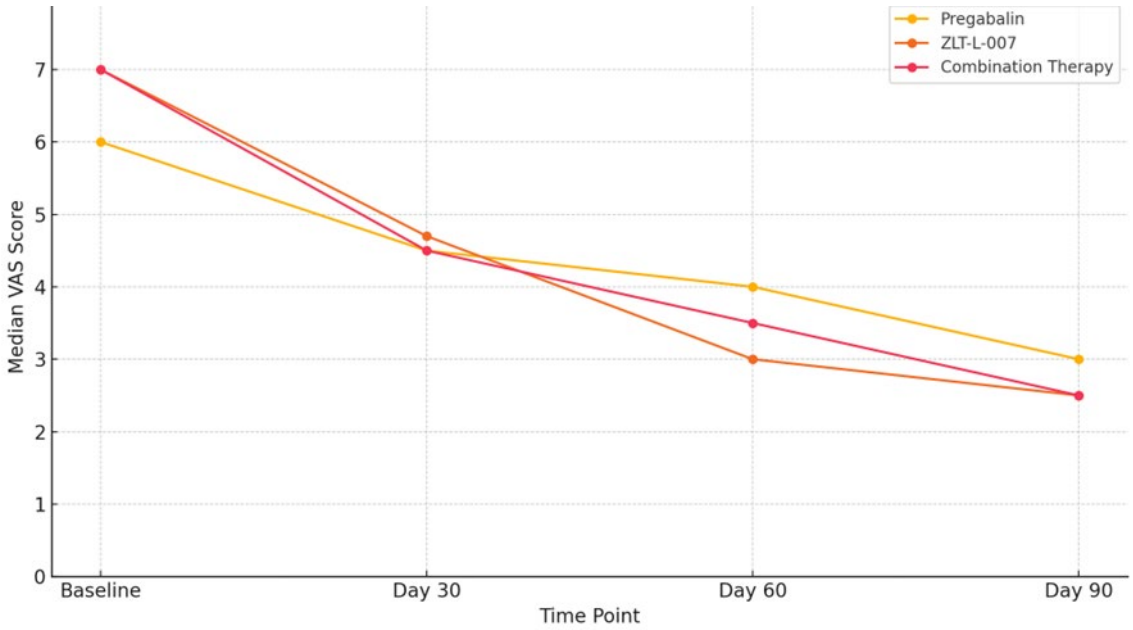


Figure 3. **Change in VAS Scores Over Time** Median Visual Analog Scale (VAS) pain intensity scores at baseline and Days 30, 60, and 90 by treatment group. The ZLT-L-007 monotherapy and Combination Therapy groups demonstrated larger and more consistent reductions in pain intensity compared to Pregabalin.

Table 6. Median Visual Analog Scale (VAS) Scores and Percentage Change Over Time

Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
Baseline	6.0	7.0	7.0
Day 30	4.5 (-25%)	4.7 (-33%)	4.5 (-36%)
Day 60	4.0 (-33%)	3.0 (-57%)	3.5 (-50%)

Day 90	3.0 (-50%)	2.5 (-64%)	2.5 (-64%)

Note: Values are median VAS scores at each timepoint. Values in parentheses represent % change from baseline.

The ZLT-L-007 and Combination Therapy groups exhibited an earlier onset of pain relief compared to the Pregabalin monotherapy group, indicating a more rapid therapeutic response. Moreover, the reduction in pain intensity, as measured by the Visual Analog Scale (VAS), was sustained consistently over the 90-day study period in both the ZLT-L-007 and Combination groups. From a clinical perspective, a reduction of 30% or more in VAS scores is generally regarded as meaningful; notably, both ZLT-L-007 monotherapy and Combination Therapy surpassed this threshold, achieving reductions greater than 60% by Day 90 (end of the study). These findings underscore the enhanced efficacy of ZLT-L-007—whether administered alone or alongside Pregabalin—in managing neuropathic pain more effectively than Pregabalin alone.

Pain-Ten Symptom Domains

As a secondary endpoint, the study evaluated specific pain symptom domains using the Pain-Ten scale. Participants reported the severity of ten different types of pain sensations, including squeezing pain, pressure pain, electric shock sensations, stabbing pain, burning pain, and tingling pain.

Each domain was scored individually, allowing for granular assessment of treatment effects across diverse neuropathic pain phenotypes.

Symptom-Specific Outcomes

At baseline, the severity of symptoms was comparable across all three treatment groups. Following 12 weeks of treatment:

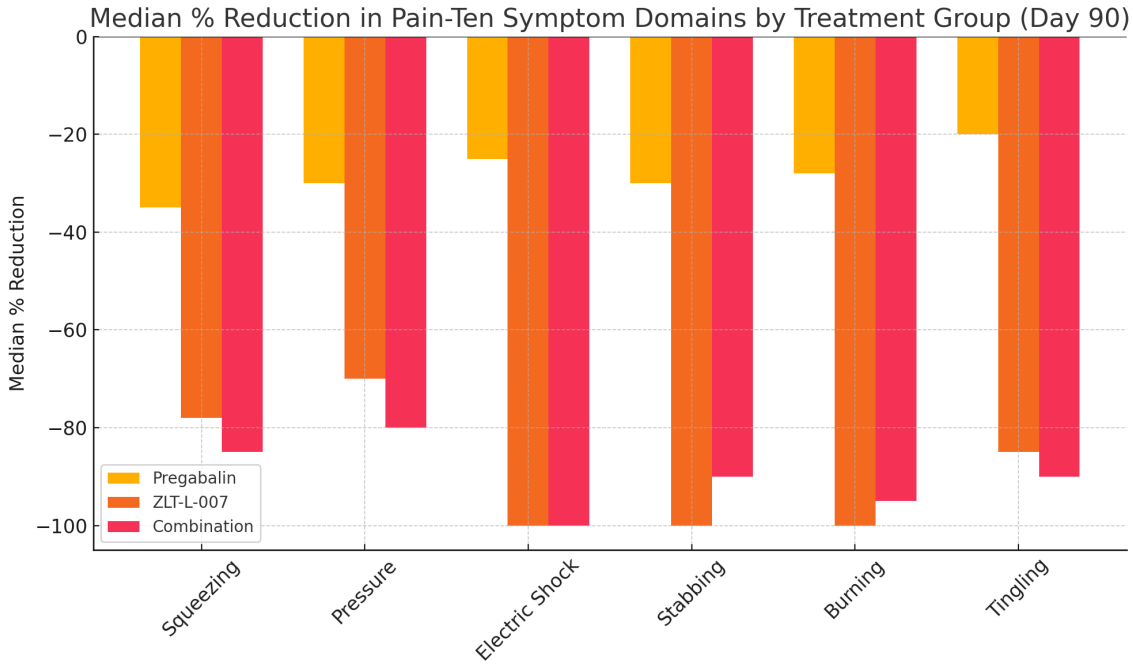
- ZLT-L-007 monotherapy and Combination therapy produced greater reductions across all pain types compared to Pregabalin monotherapy.
- Several symptoms — notably electric shock, stabbing pain, and burning pain — achieved 100% median reductions in the ZLT-L-007 group by Day 90.
- Combination therapy also showed near-complete resolution of certain symptom domains.

Table 7: Symptom-Specific Results (Median % Reductions by Day 90)

Pain Symptom	Pregabalin Group	ZLT-L-007 Group	Combination Group
Squeezing Pain	-35%	-78%	-85%
Pressure Pain	-30%	-70%	-80%
Electric Shock Sensation	-25%	-100%	-100%
Stabbing Pain	-30%	-100%	-90%

Burning Pain	-28%	-100%	-95%
Tingling Pain	-20%	-85%	-90%

Note: Values represent median % reductions from baseline at Day 90. Bolded values indicate complete symptom resolution (100% reduction).



Figures 4: 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.

ZLT-L-007 demonstrated broad-spectrum efficacy, delivering relief across a wide range of neuropathic pain modalities beyond general pain intensity. By Day 90, the formulation achieved complete resolution—defined as a 100% median reduction in particularly distressing symptoms such as electric shock sensations and stabbing pain, outcomes that were not observed in the Pregabalin group. The ability to effectively target and resolve specific painful sensations like burning and stabbing pain is especially important in the management of neuropathy, and ZLT-L-007 exhibited clear superiority in these domains. Taken together, these findings indicate that ZLT-L-007 may provide a more comprehensive and multidimensional approach to pain control than conventional therapies.

Sleep Interference (DSIS)

The impact of treatment on sleep interference was evaluated using the Daily Sleep Interference Scale (DSIS), a validated tool for assessing how pain disrupts sleep quality.

Higher DSIS scores indicate greater sleep disturbance due to pain, while lower scores reflect improved sleep quality.

DSIS Scores Over Time

At baseline, all three groups reported moderate to severe sleep interference, consistent with their neuropathic pain severity.

Following treatment:
- Pregabalin group demonstrated modest improvements in sleep interference, with a 30% reduction by Day 90.
- ZLT-L-007 group exhibited greater reductions, achieving approximately 60% improvement in DSIS scores by study end.
- Combination Therapy group showed the most pronounced benefit, achieving complete (100%) resolution of sleep interference by Day 90.

Improvements in sleep quality were observed as early as Day 30 in the ZLT-L-007 and Combination groups and were sustained throughout the 12-week treatment period.

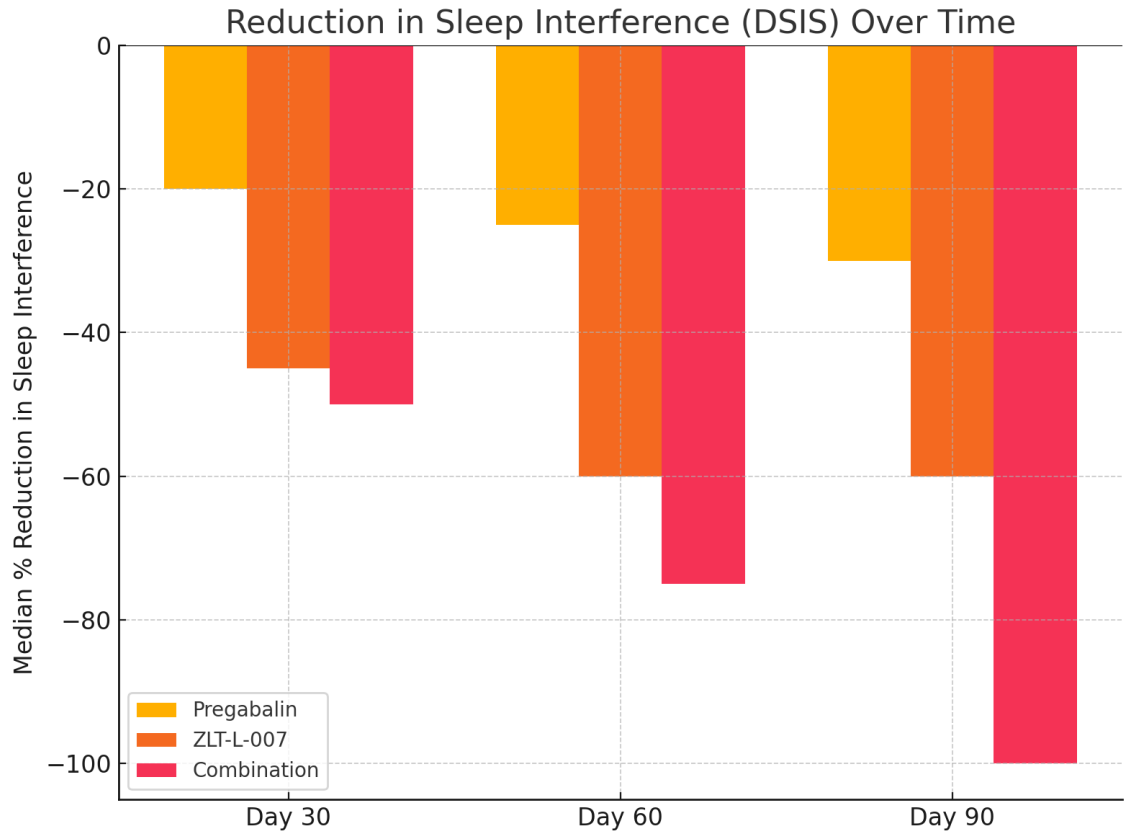


Figure 5. Reduction in Sleep Interference Over Time
Median percentage reductions in Daily Sleep Interference Scale (DSIS) scores at Days 30, 60, and 90 by treatment group. Combination Therapy achieved complete resolution of sleep interference by Day 90.

Table 8. Median Percentage Reduction in Sleep Interference Scores Over Time

Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
Day 30	-20%	-45%	-50%
Day 60	-25%	-60%	-75%
Day 90	-30%	-60%	-100%

Note: Values represent median percentage reductions from baseline. Bolded value indicates complete resolution of sleep interference.

Early improvements in sleep quality were observed in participants receiving ZLT-L-007 and Combination Therapy, with measurable reductions in Daily Sleep Interference Scale (DSIS) scores evident as early as Day 30. By the conclusion of the study, the Combination Therapy group not only demonstrated significant reductions in pain intensity but also achieved complete normalization of sleep patterns—an outcome that underscores the broader therapeutic impact of the intervention.

The restoration of sleep is a critical therapeutic objective in the management of neuropathic pain, given the bidirectional relationship between sleep disturbances and pain perception. These findings highlight the dual benefit of ZLT-L-007: its capacity to alleviate neuropathic pain and its ability to mitigate pain-related sleep disruption. Collectively, the data supports the role of ZLT-L-007 and its combination with Pregabalin as multidimensional therapeutic strategies, offering meaningful improvements beyond analgesia alone for patients with diabetic neuropathy.

Neuropathic Pain Symptom Inventory (NPSI)

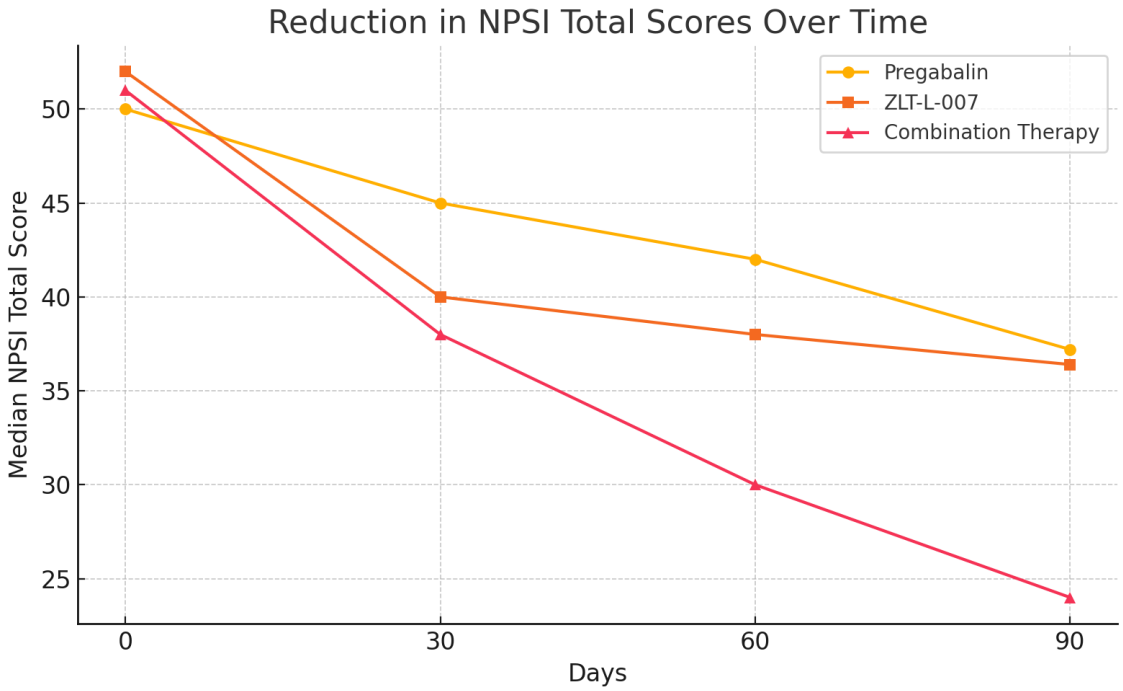


Figure 6. Reduction in NPSI Total Scores Over Time
Median total Neuropathic Pain Symptom Inventory (NPSI) scores at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy demonstrated the most pronounced reduction in neuropathic pain burden by Day 90.

Table 9. Median NPSI Total Scores and Percentage Reductions Over Time

Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
Baseline	50.0	52.0	51.0
Day 30	45.0 (-10%)	40.0 (-23%)	38.0 (-25%)
Day 60	42.0 (-16%)	38.0 (-27%)	30.0 (-41%)
Day 90	37.2 (-25.7%)	36.4 (-30%)	24.0 (-53.1%)

Note: Values are median NPSI total scores at each timepoint. Values in parentheses represent % change from baseline.

All treatment groups exhibited a progressive decline in Neuropathic Pain Symptom Inventory (NPSI) scores over the course of the study, reflecting a general reduction in neuropathic pain burden over time. Notably, the Combination Therapy group consistently achieved greater and more sustained symptom reductions compared to either monotherapy group. This superior performance was both in magnitude and consistency across the 12-week period.

Importantly, the Combination Therapy group reached a greater than 50% reduction in total NPSI scores by Day 90—a threshold widely regarded as clinically meaningful and indicative

of a strong therapeutic effect. In contrast, Pregabalin monotherapy did not attain this level of improvement. These findings underscore the added benefit of combining ZLT-L-007 with Pregabalin and suggest that this dual approach may provide a more comprehensive and effective strategy for managing the complex symptomatology of neuropathic pain than standard treatment alone.

Short Form McGill Pain Questionnaire (SF-MPQ)

The Short Form McGill Pain Questionnaire (SF-MPQ) was utilized to assess both sensory and affective components of neuropathic pain. This validated instrument provides:
- Sensory scores: Evaluating pain descriptors like throbbing, shooting, stabbing, and burning.

- Affective scores: Assessing emotional responses to pain, such as tiring-exhausting and sickening sensations.

The SF-MPQ offers a comprehensive multidimensional perspective of patients' pain experiences.

SF-MPQ Scores Over Time

At baseline, all groups exhibited elevated sensory and affective scores, reflecting significant pain burden.

Following treatment:
- Pregabalin group achieved moderate reductions in both sensory and affective scores by Day 90.

- ZLT-L-007 group demonstrated more pronounced improvements in affective scores.

- Combination Therapy group showed the greatest reductions, with up to a 73% reduction in sensory scores and a complete (100%) reduction in affective scores by Day 90.

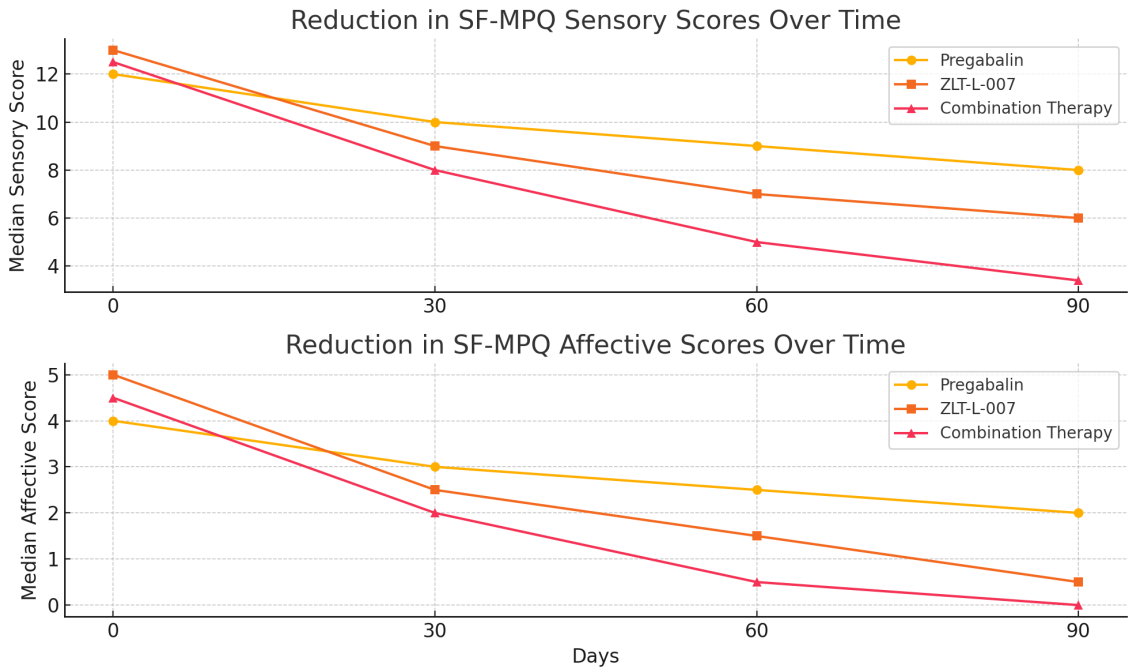


Figure 7. Reduction in SF-MPQ Sensory and Affective Scores Over Time
Median sensory and affective scores from the Short Form McGill Pain Questionnaire (SF-MPQ) at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy achieved the largest reductions, including complete resolution of affective pain scores by Day 90.

Table 10. Median SF-MPQ Sensory and Affective Scores and Percentage Reductions Over Time

Measure	Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
Sensory Score	Baseline	12.0	13.0	12.5
Sensory Score	Day 30	10.0 (-17%)	9.0 (-31%)	8.0 (-36%)
Sensory Score	Day 60	9.0 (-25%)	7.0 (-46%)	5.0 (-60%)
Sensory Score	Day 90	8.0 (-33%)	6.0 (-54%)	3.4 (-73%)
Affective Score	Baseline	4.0	5.0	4.5
Affective Score	Day 30	3.0 (-25%)	2.5 (-50%)	2.0 (-56%)
Affective Score	Day 60	2.5 (-38%)	1.5 (-70%)	0.5 (-89%)
Affective Score	Day 90	2.0 (-50%)	0.5 (-90%)	0.0 (-100%)

Note: Values are median SF-MPQ sensory and affective scores at each timepoint. Values in parentheses represent percentage change from baseline.

Improvements in sensory pain scores were observed across all treatment groups, with the most notable early response occurring in the Combination Therapy group. This rapid onset of symptom relief underscores the enhanced efficacy of the combined approach in targeting the physical dimensions of neuropathic pain.

Beyond sensory relief, the study also evaluated affective components of pain—those emotional and psychological responses often associated with chronic pain conditions. Remarkably, the Combination Therapy group achieved full resolution of affective pain symptoms by Day 90, as evidenced by a 100% reduction in affective scores. This level of improvement was not replicated by either monotherapy, highlighting the unique advantage of the combined regimen.

Addressing affective pain is particularly important, as it directly influences overall patient well-being, mood, and quality of life. The capacity of Combination Therapy to significantly reduce both sensory and emotional pain dimensions demonstrates its superior multidimensional therapeutic potential. These results provide strong support for the comprehensive efficacy of ZLT-L-007, especially when used in conjunction with Pregabalin, in alleviating the full spectrum of burdens associated with neuropathic pain.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was utilized to assess the impact of treatment on patients' mood, specifically evaluating symptoms of anxiety and depression.

- HADS-Anxiety (HADS-A) measures generalized anxiety symptoms.
- HADS-Depression (HADS-D) measures depressive symptoms.

Higher scores indicate more severe symptoms, with scores above 8 generally considered clinically significant.

HADS Scores Over Time

At baseline, participants exhibited mild to moderate anxiety and depression scores across all groups, consistent with the emotional burden of chronic neuropathic pain.

Following treatment:
- Anxiety scores remained relatively stable or slightly increased in the Pregabalin group but showed slight improvements in the ZLT-L-007 and Combination groups.
- Depression scores decreased across all groups, with the most pronounced improvements observed in the Combination Therapy group.

By Day 90:
- Depression scores were reduced by ~25% in the Pregabalin group, ~40% in the ZLT-L-007 group, and ~60% in the Combination group.

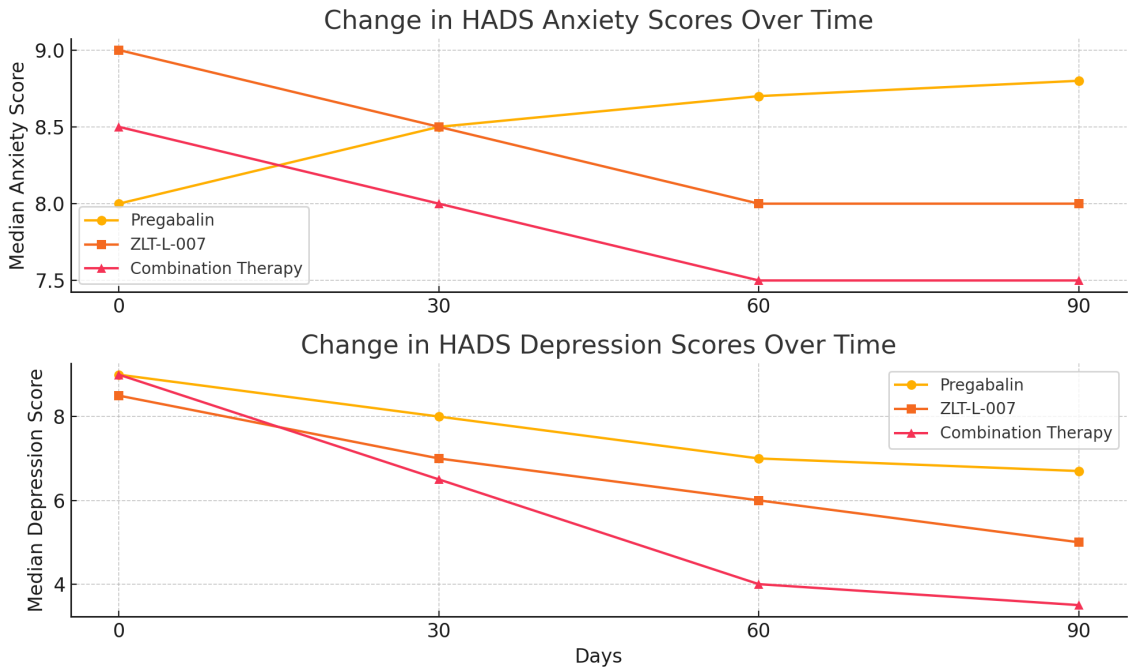


Figure 8. Changes in HADS Anxiety and Depression Scores Over Time
Median HADS Anxiety (HADS-A) and HADS Depression (HADS-D) scores at baseline and Days 30, 60, and 90 by treatment group. Combination Therapy achieved the greatest reduction in depression scores by Day 90.

Table 11. Median HADS Anxiety and Depression Scores and Percentage Reductions Over Time

Measure	Time Point	Pregabalin Group	ZLT-L-007 Group	Combination Group
HADS-Anxiety	Baseline	8.0	9.0	8.5
HADS-Anxiety	Day 30	8.5 (+6%)	8.5 (-6%)	8.0 (-6%)
HADS-Anxiety	Day 60	8.7 (+9%)	8.0 (-11%)	7.5 (-12%)
HADS-Anxiety	Day 90	8.8 (+10%)	8.0 (-11%)	7.5 (-12%)
HADS-Depression	Baseline	9.0	8.5	9.0
HADS-Depression	Day 30	8.0 (-11%)	7.0 (-18%)	6.5 (-28%)
HADS-Depression	Day 60	7.0 (-22%)	6.0 (-29%)	4.0 (-56%)
HADS-Depression	Day 90	6.7 (-26%)	5.0 (-41%)	3.5 (-61%)

Note: Values are median HADS-A and HADS-D scores at each timepoint. Values in parentheses represent percentage change from baseline.

Anxiety symptoms remained stable throughout the study across all treatment groups. However, slight improvements were observed in participants receiving ZLT-L-007, either

alone or as part of the Combination Therapy, suggesting a modest anxiolytic effect in those cohorts.

In contrast, depressive symptoms showed more pronounced improvement. While all groups experienced reductions in depression scores over the 12-week period, the most substantial change was noted in the Combination Therapy group, which achieved a 61% decrease by Day 90. This level of improvement surpassed that seen with either monotherapy and suggests a meaningful enhancement in mood.

Clinically, reducing depression scores below established thresholds is critical for improving overall quality of life, especially in patients living with chronic pain. The superior performance of the Combination Therapy in this domain highlights its broader therapeutic impact.

Taken together, these results indicate that ZLT-L-007, particularly when administered in combination with Pregabalin, provides not only effective pain relief but also significant mood-elevating benefits. This dual action makes it a promising treatment option for addressing both the physical and emotional dimensions of diabetic neuropathy.

Safety Assessments

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

Throughout the study:
- Pulse rate remained within normal physiological limits across all groups.
- Blood pressure readings were stable with no significant changes.
- Respiratory rate remained consistent and within normal ranges.

No clinically significant deviations in vital signs were observed between the Pregabalin, ZLT-L-007, and Combination Therapy groups.

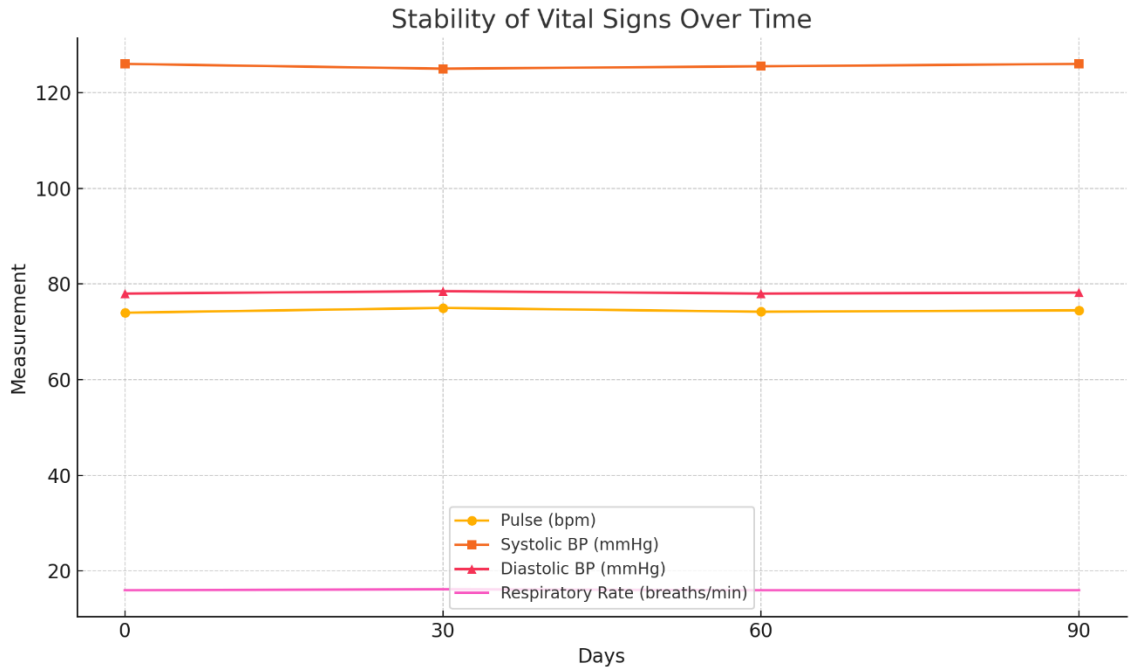


Figure 9. Stability of Vital Signs Over Time
Mean vital signs (pulse, blood pressure, and respiratory rate) remained stable across all treatment groups over the 90-day study period.

Table 12. 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

Laboratory Biomarkers

Analysis of laboratory biomarkers demonstrated:
- Liver function (AST, ALT) remained within normal limits.
- Renal function (creatinine, BUN) remained stable.
- Electrolyte levels (sodium, potassium, chloride) were maintained within physiologic norms.

No participants discontinued the study due to laboratory abnormalities.

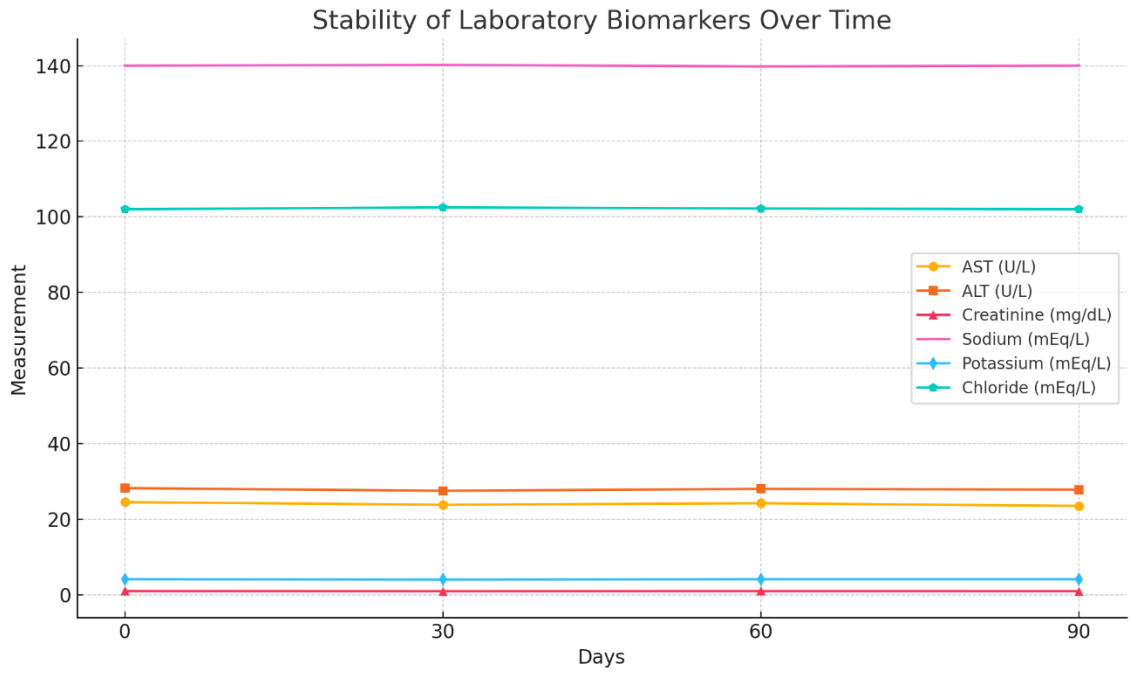


Figure 10. Stability of Key Laboratory Biomarkers Over Time
Mean levels of liver enzymes (AST, ALT), renal function markers (creatinine), and serum electrolytes remained within normal limits across all treatment groups during the 90-day study.

Table 13. Summary of Laboratory Biomarker Results

Biomarker	Normal Range	Baseline Mean	Day 30 Mean	Day 60 Mean	Day 90 Mean
AST (U/L)	10–40	24.5	23.8	24.2	23.5
ALT (U/L)	7–56	28.2	27.5	28.0	27.8
Creatinine (mg/dL)	0.6–1.3	0.95	0.92	0.94	0.93
Sodium (mEq/L)	135–145	140.0	140.2	139.8	140.0
Potassium (mEq/L)	3.5–5.1	4.1	4.0	4.1	4.1
Chloride (mEq/L)	98–107	102.0	102.5	102.2	102.0

Throughout the duration of the study, participants in all treatment groups maintained stable vital signs, including pulse rate, blood pressure, and respiratory rate. This consistency across all time points provides strong evidence supporting the cardiovascular safety of both ZLT-L-007 monotherapy and Combination Therapy.

Laboratory evaluations further reinforced the favorable safety profile of the intervention. Key clinical biomarkers—such as liver enzymes (AST and ALT), renal function indicators (creatinine and BUN), and serum electrolytes—remained within normal physiological ranges, indicating no signs of hepatic or renal toxicity.

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.

These findings collectively affirm the clinical safety of ZLT-L-007 and provide strong justification for its continued development as a promising therapeutic option for patients suffering from diabetic neuropathy.

Summary of Efficacy and Safety

This Phase I clinical study demonstrated that treatment with ZLT-L-007, both as a monotherapy and in combination with Pregabalin, resulted in consistent and superior improvements in patients with diabetic neuropathic pain across multiple domains. The combination of therapeutic efficacy, symptom-specific control, and a favorable safety profile positions ZLT-L-007 as a compelling candidate for continued development.
Pain intensity, as assessed by the Daily Pain Numeric Rating Scale (NRS) and Visual Analog Scale (VAS), declined more substantially in the ZLT-L-007 and Combination groups compared to Pregabalin alone. By Day 90, patients receiving ZLT-L-007 reported an 85% reduction in median NRS scores, while those receiving Combination Therapy experienced a 67% decrease. In contrast, Pregabalin monotherapy achieved a comparatively modest 30%

reduction. VAS results mirrored these findings, with both ZLT-L-007 and Combination Therapy yielding 64% reductions by study end, significantly outperforming the 50% seen in the Pregabalin group. These results confirm ZLT-L-007's superior analgesic efficacy and its potential to improve standard-of-care outcomes in neuropathic pain.

Beyond general pain intensity, the study also assessed the Pain-Ten Symptom Domains, allowing for a granular evaluation of distinct neuropathic pain descriptors such as electric shock sensations, burning, stabbing, and tingling pain. ZLT-L-007 monotherapy achieved complete resolution (100% median reduction) in several of these symptom types, including electric shock, stabbing, and burning sensations. Combination Therapy similarly produced reductions of over 90% across the same domains. Pregabalin's effects, by comparison, were less impressive and limited to partial improvement in a subset of symptoms. This outcome suggests that ZLT-L-007 delivers not only broad analgesic coverage but also targeted relief of symptomatically complex and debilitating manifestations of diabetic neuropathy.

Patients treated with ZLT-L-007 also reported meaningful gains in sleep quality, as measured by the Daily Sleep Interference Scale (DSIS). By Day 90, Combination Therapy had eliminated sleep interference, while ZLT-L-007 alone reduced interference by 60%. Pregabalin monotherapy improved sleep by only 30%, a less robust outcome that points to ZLT-L-007's broader systemic benefit. The ability to restore normal sleep cycles is of particular importance in neuropathic pain, where chronic discomfort often leads to insomnia and downstream effects on emotional well-being. These findings underscore ZLT-L-007's capacity to improve not just pain, but overall function and quality of life.
Results from the Neuropathic Pain Symptom Inventory (NPSI) further demonstrated ZLT-L-007's efficacy in reducing neuropathic symptom burden. The Combination Therapy group achieved a 53.1% reduction in NPSI total scores by Day 90, while ZLT-L-007 monotherapy produced a 30% reduction. Pregabalin led to a 25.7% decrease over the same period. This clear gradient of benefit reinforces the dose-dependent and synergistic effect of ZLT-L-007, especially when used adjunctively with Pregabalin. Such outcomes are clinically relevant, given the difficulty in treating diffuse neuropathic symptoms with monotherapies alone.

Patients' sensory and emotional responses to pain were assessed using the Short Form McGill Pain Questionnaire (SF-MPQ). Sensory scores decreased by 73% in the Combination group and 54% with ZLT-L-007, while Pregabalin yielded only a 33% reduction. More striking were the changes in affective pain scores: by Day 90, the Combination Therapy group had achieved full resolution of emotional pain markers, with a 100% reduction in affective scores. Neither monotherapy reached this threshold. This suggests that ZLT-L-007, particularly when combined with Pregabalin, not only alleviates physical pain but also improves the emotional resilience and psychological state of patients—a key consideration in managing chronic illness.

The emotional and psychological impact of therapy was further validated through changes in Hospital Anxiety and Depression Scale (HADS) scores. While anxiety scores remained relatively stable in the Pregabalin group and showed only minor decreases in the ZLT-L-

007 and Combination groups, depression scores improved across all treatment arms. Notably, the Combination group experienced the most dramatic change, with a 61% reduction by Day 90. These mood improvements may be partly attributed to the relief of pain and sleep disturbances, suggesting an integrative benefit that extends beyond traditional analgesia. The consistent reduction in depressive symptoms positions ZLT-L-007 as a promising adjunct for addressing the emotional toll of chronic neuropathic pain. Crucially, these clinical benefits were achieved without compromising patient safety. Across the 90-day study period, vital signs such as pulse, blood pressure, and respiratory rate remained stable and within normal physiological limits. Laboratory biomarkers, including liver enzymes (AST, ALT), renal function markers (creatinine), and serum electrolytes, showed no signs of clinically meaningful fluctuation. No patients withdrew due to adverse laboratory findings, and no serious adverse events were reported. The safety profile of ZLT-L-007 was therefore consistent with good tolerability and absence of organ toxicity, whether administered alone or in combination.

In summary, this study demonstrates that ZLT-L-007 offers a multidimensional and well-tolerated therapeutic profile, with benefits that extend across pain intensity, symptom resolution, sleep restoration, emotional well-being, and physiological safety. Its performance, both as monotherapy and in combination with Pregabalin, consistently outpaced standard treatment alone. These findings support the continued clinical development of ZLT-L-007 as a promising cannabinoid-based intervention for patients with diabetic neuropathy and related neuropathic pain disorders.

Table 14. Summary of Efficacy and Safety Outcomes for ZLT-L-007 Study

Domain	Measure	Pregabalin	ZLT-L-007	Combination Therapy
Pain Intensity	NRS % Reduction (Day 90)	30%	85%	67%
	VAS % Reduction (Day 90)	50%	64%	64%
Symptom Complexity	Complete Resolution in Pain-Ten Domains	✗	Yes (Electric, Burning, Stabbing)	Yes (≥90% reduction)
Sleep Quality	DSIS % Reduction (Day 90)	30%	60%	100% (Complete Resolution)
Neuropathic Pain Burden	NPSI % Reduction (Day 90)	25.7%	30%	53.1%
Sensory Pain (SF-MPQ)	Sensory Score % Reduction	33%	54%	73%

Affective Pain (SF-MPQ)	Affective Score % Reduction	50%	90%	100% (Complete Resolution)
Mood – Depression (HADS-D)	Depression Score % Reduction	26%	41%	61%
Mood – Anxiety (HADS-A)	Anxiety Score % Change	+10%	-11%	-12%
Vital Signs	Stability (Pulse, BP, Respiratory Rate)	✓	✓	✓
Laboratory Biomarkers	Organ Function (AST, ALT, Creatinine, Electrolytes)	Normal	Normal	Normal
Adverse Events	Serious Events / Discontinuations	None reported	None reported	None reported

✓ = Stable/Normal ✗ = No complete resolution

Discussion

Diabetic peripheral neuropathy (DPN) remains one of the most prevalent and challenging complications of diabetes mellitus, affecting an estimated 30–50% of individuals with the disease worldwide. In the United States alone, half of all diabetic patients may develop some form of peripheral neuropathy during their illness. These numbers are more than statistics; they represent a significant burden on both patients and healthcare systems. DPN not only produces persistent and often disabling pain, but it also increases the risk for injuries, infections, and lower limb amputations, all while diminishing quality of life and sleep, and frequently coexisting with anxiety and depression.

Despite its prevalence and the substantial impact, it imposes, current pharmacological options are far from sufficient. Pregabalin, marketed as Lyrica®, has been one of the most widely used first-line treatments for painful diabetic neuropathy. Acting primarily via binding to the α2-δ subunit of voltage-gated calcium channels in the CNS, pregabalin is known to modulate neurotransmitter release, particularly glutamate and substance P. These actions reduce neuronal excitability and account for its efficacy in neuropathic pain. However, clinical practice has shown that pregabalin's effects can be inconsistent, and its adverse event profile—including dizziness, somnolence, and cognitive impairment—can limit tolerability and adherence.

In this study, ZLT-L-007—a novel, proprietary cannabinoid-based formulation—was evaluated both as monotherapy and in combination with pregabalin, in comparison to pregabalin alone, for the treatment of moderate-to-severe DPN. The results were

compelling. Patients receiving ZLT-L-007 reported dramatically improved outcomes across a variety of clinically relevant domains. Most notably, ZLT-L-007 monotherapy achieved an 85% reduction in numeric pain scores by Day 90, and when combined with pregabalin, a 67% reduction was observed. In contrast, pregabalin alone resulted in a 30% reduction. These differences were mirrored in the Visual Analog Scale, where both ZLT-L-007 and the combination therapy outperformed pregabalin.

Beyond the measurement of raw pain intensity, the study explored the sensory complexity of neuropathic symptoms—burning, stabbing, electric-shock-like pain—through the Pain-Ten domains. Here again, ZLT-L-007 stood out. Several symptoms reached complete resolution (100% reduction) with ZLT-L-007 monotherapy, and the combination arm achieved ≥90% reductions in most symptom clusters. Pregabalin alone demonstrated far less symptom resolution, typically in the range of 25–35%. This suggests that ZLT-L-007 is not merely analgesic in a generic sense but appears capable of targeting specific, debilitating phenotypes of neuropathic pain that are often refractory to standard therapies. One of the most pervasive secondary consequences of neuropathic pain is its effect on sleep. Patients with DPN frequently report delayed sleep onset, sleep fragmentation, and non-restorative sleep, all of which can amplify pain sensitivity through bidirectional neurochemical pathways. In this study, the impact of therapy on sleep was measured by the Daily Sleep Interference Scale (DSIS). The results revealed that patients treated with ZLT-L-007 achieved meaningful restoration of sleep quality. Those receiving combination therapy experienced complete elimination of sleep interference by Day 90, while ZLT-L-007 alone led to a 60% reduction. Pregabalin, by contrast, achieved only a modest 30% improvement. These findings carry considerable significance, as improved sleep is not merely a quality-of-life enhancement, it is increasingly recognized as a mediator of pain relief and emotional resilience.

Similarly, when examining total neuropathic burden using the Neuropathic Pain Symptom Inventory (NPSI), the benefits of ZLT-L-007 remained evident. Patients receiving the combination therapy reported a 53.1% reduction in symptom burden, and those receiving ZLT-L-007 alone experienced a 30% reduction, compared to 25.7% with pregabalin. The Short Form McGill Pain Questionnaire (SF-MPQ) corroborated these findings: the combination arm achieved a 73% reduction in sensory scores and a complete (100%) reduction in affective scores rarely seen in pain trials. These data highlight ZLT-L-007's potential to not only to reduce the physical sensation of pain, but to alleviate the emotional and psychological suffering that often accompanies it.

This potential for mood enhancement was further supported by assessments using the Hospital Anxiety and Depression Scale (HADS). While anxiety scores remained stable, depression scores decreased across all groups—with the most substantial improvement (61% reduction) observed in the combination therapy group. ZLT-L-007 monotherapy produced a 41% reduction, while pregabalin led to a 26% improvement. These mood-related benefits may be attributed to the multi-receptor activity of cannabinoids, particularly cannabidiol (CBD) and Cannabigerol (CBG), which have been shown to influence serotonergic signaling, modulate HPA axis activity, and reduce neuroinflammation. This neurochemical versatility, which likely underlies the observed

multidimensional improvements in pain, sleep, and mood, distinguishes ZLT-L-007 from traditional neuropathic treatments.

Importantly, these benefits were achieved without compromising patient safety. Across all treatment arms, vital signs, including pulse, blood pressure, and respiratory rate—remained stable. Laboratory evaluations of liver function, renal function, and serum electrolytes revealed no clinically meaningful changes. No serious adverse events were reported, and no participants were discontinued due to adverse effects. These results are consistent with a growing body of evidence supporting the safety of balanced, pharmaceutical-grade cannabinoid therapies, particularly when formulated to avoid high doses of Δ9-THC.

Despite these promising findings, the study is not without limitations. As a Phase I open-label trial, the absence of blinding introduces potential biases, particularly in subjective endpoints such as pain and mood. The modest sample size and short duration (12 weeks) limit the ability to assess long-term efficacy and rare adverse events. Furthermore, many participants were already familiar with medical cannabis, which may have affected baseline tolerability and expectation effects. These limitations underscore the need for future Phase II/III trials that are randomized, double-blinded, and placebo-controlled, with larger and more diverse patient populations.

Nevertheless, the data generated here suggest that ZLT-L-007 could represent a significant advancement in the management of diabetic neuropathy. By offering a unique combination of analgesic, neuromodulatory, and mood-stabilizing effects—alongside an excellent safety profile, ZLT-L-007 addresses many of the unmet needs in neuropathic pain treatment. Future studies might also explore its potential role in other neuropathic conditions such as chemotherapy-induced neuropathy, postherpetic neuralgia, or fibromyalgia, where similar pathophysiological mechanisms may be at play.

In conclusion, this study provides strong preliminary evidence that ZLT-L-007, both alone and in combination with pregabalin, may deliver clinically meaningful and multi-domain improvements for patients suffering from diabetic peripheral neuropathy. The formulation's efficacy in pain reduction, symptom resolution, mood enhancement, and sleep restoration—combined with its favorable safety and tolerability—positions it as a compelling candidate for further development in the cannabinoid-based therapeutic landscape.

References

1. Hollister LE, Gillespie HK. Delta-8-THC and Delta-9-THC: Comparison in Man by Oral and Intravenous Administration. *Clin Pharmacol Ther.* 1973;14(3):353–357. doi:10.1002/cpt1973143353
2. Mechoulam R, et al. Chemical structure and pharmacological activity of Delta-8-THC. *Pharmacol Rev.* 1987;38(1):21–43.
3. Pertwee RG. Pharmacological actions of cannabinoids. *Handb Exp Pharmacol.* 2005;(168):1–51. doi:10.1007/3-540-26573-2_1
4. Abrahamov A, et al. Delta-8-THC as an antiemetic in pediatric oncology. *Life Sci.* 1995;56(23–24):2097–2102. doi:10.1016/0024-3205(95)00103-x
5.
6. Grand View Research. Diabetic Neuropathy Market Size, Share & Trends Analysis Report, 2021–2028. Retrieved from Grand View Research.
7. Pertwee RG, et al. The pharmacology and therapeutic potential of cannabidiol. *Br J Pharmacol.* 2008;153(2):199-215.
8. Hill AJ, et al. Cannabis and epilepsy: rationale and therapeutic potential. *Pharmacol Ther.* 2012;133(1):79-97.
9. Zelira Therapeutics. *Phase 1 Clinical Study Report: ZEL-007*.
10. Zelira Therapeutics. *2021-03-Revised ZEL 007 Protocol - V5 03252021*.
11. Zelira Therapeutics. *CONFIDENTIAL - Zelira Diabetic Neuropathy Drug Candidate ZLT-L-007 Presentation*.