Shifting the Paradigm to a Biomarker Focused Approach for Developing an Amyotrophic Lateral Sclerosis (ALS) Therapy

Shiran Zimri[1], Nitai Kerem[1], Niva Russek-Blum[1], Andrew Thompson[2], Jacob Harris[2], Jin Xu[2], Hiu Ying Nicole Wong[2], Craig Lawless[2], Martin Bachman[2], Ernestas Sirka[2] & Ferenc Tracik[1]

[1]NeuroSense Therapeutics, Ltd, Herzliya, Israel | [2]Inoviv, London, United Kingdom

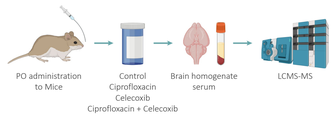
PrimeC: A Novel Combination Therapy Approach

ALS therapy remains a highly unmet need due to the heterogeneity and the complexity of the disease. Multiple pathways are involved, and monotherapy has not been shown to elicit a meaningful impact. Therefore, a new approach is needed. We believe that the most effective way to tackle ALS is on multiple fronts. PrimeC is a unique combination therapy assembled of two FDA approved drugs, ciprofloxacin and celecoxib, aiming to work synergistically on more than one key target.

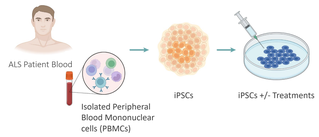
Utilizing combination therapy holds two main advantages: (i) Improving pharmacokinetics; (ii) Enhancing the compounds' mechanism of action. PrimeC addresses both domains.

The following assays has been conducted to elucidate the Synergistic effect of PrimeC:

1. **Assessing the effect of combination treatment on Pharmacokinetic (PK) Profile**



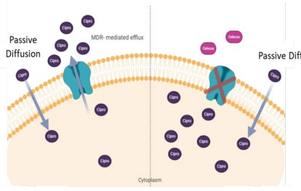
2. **Assessing the effect of combination treatment on ALS-related pathologies**



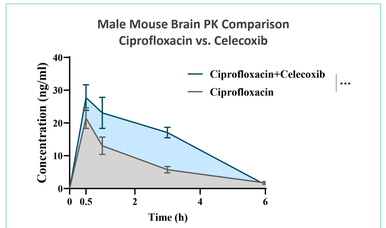
Collaboration with Dr. Justin Ichida, University of Southern California

Improved Pharmacokinetics:

Results obtained from pharmacokinetic studies in rodents demonstrate the synergistic effect between the two compounds, as the addition of celecoxib increased the concentration of ciprofloxacin in rodent brain tissue. The unique extended-release formulation of PrimeC allows us to maximize their synergism.



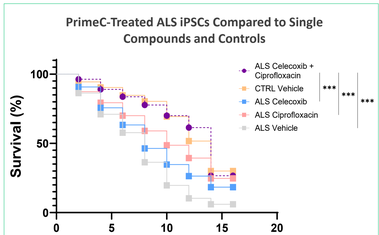
This finding is attributed to **celecoxib** blocking the exit of **ciprofloxacin** from the neuron



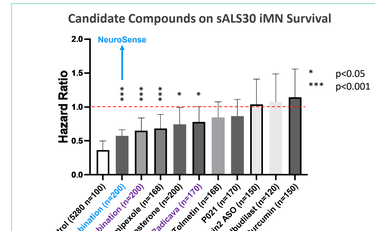
PrimeC's combination (**celecoxib + ciprofloxacin**) **remained at a higher concentration in rodent brain tissue for longer**, when compared to administration of **ciprofloxacin alone**

Improved Efficacy:

An iPSC model collaboration study revealed exceeded survival rates of neurons treated with PrimeC compared to neurons treated with each of its comprising compounds. PrimeC-treated cells also demonstrated enhanced survival rates compared to other available ALS therapies.



In collaboration with Dr. Justin Ichida



Independent, non-sponsored research was conducted in the laboratory of Dr. Justin Ichida

PrimeC Phase 2a: Open-Label, PoC Study

NST002

15 patients
Open-Label
Intermediate formulation of PrimeC
12-month dosing
Clinic visit every **3** months
Phone visit every **1.5** months

Location: Tel Aviv Sourasky Medical Center

- Well tolerated, no drug related SAEs
- Reduced functional and respiratory deterioration
- Significant changes in ALS-related biomarkers

These results led NeuroSense to commence a Phase 2b clinical study, using an improved new extended-release formulation of PrimeC

Phase 2a Trial with PrimeC:

Met Primary Endpoints & Exploratory Endpoints. Positive Clinical Measures Observed

PARADIGM SHIFTING THE PARADIGM

NST003

69 patients enrolled
2:1 PrimeC to Placebo
New formulation of PrimeC
6-month double blind
12-month open label extension
Clinic visit every **2** months
Locations: Canada, Italy, & Israel

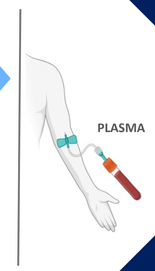
PrimeC Phase 2b: Randomized, Prospective, Double-Blind, Placebo-Controlled Study

1. **Primary Efficacy Biomarkers**
   TDP-43
   Prostagladin2
2. **Secondary Efficacy Clinical Outcomes**
   ALSFRSr
   SVC
   Survival
3. **Safety & Tolerability**
   Adverse Events
   Vital Signs
   ECG
   Clinical Lab Evaluations

PrimeC 2:1 Placebo — **Double-Blind** (2022–2023) → **PrimeC Only** — **OLE**

- First Patient In May 2022 — Israel
- First Patient In March 2023 — Torino
- First Patient In March 2023 — Milan
- First Patient In April 2023 — Canada
- Last patient Out DB Nov2023
- Top Line Results — Double Blind

96% into OLE



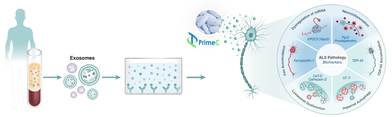
Pioneering Approach to ALS Biomarker Research

PARADIGM SHIFTING THE PARADIGM

PARADIGM Study Design

Primary and Secondary Endpoints

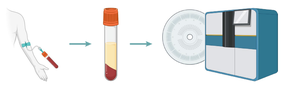
Two key biomarkers, TDP-43 and PGJ2 will be analyzed as primary outcomes. Additional biomarker-driven assays serve as exploratory endpoints, aiming to broaden the knowledge regarding ALS drug development, biological activity, and target engagement.



Neurofilaments

Neurofilament light chain (NfL), a promising biomarker for neuronal degeneration and death through monitoring disease progression, has recently demonstrated its potential as a reflector for treatment efficacy. Therefore, the ability of PrimeC to alter NfL elevation and its correlation to key clinical outcomes will be assessed.

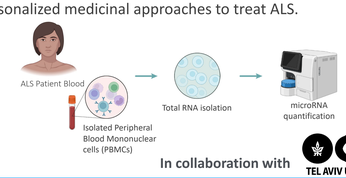
The concentrations of NfL will be assessed with the use of the Simoa NF-light advantage assay (Quanterix), and concentrations of pNfH with the use of the Simple Plex Ella Immunoassay (Protein Simple).



In collaboration with Biogen

microRNA Profiling

Profiling microRNAs holds paramount significance in tailoring treatments for ALS patients. MicroRNAs, small non-coding RNA molecules, play a pivotal role in regulating gene expression. Their dysregulation has been implicated in ALS pathogenesis. By comprehensively characterizing microRNA signatures in ALS patients, we can identify specific molecular targets crucial for disease progression. This enables the development of more precise, RNA-based therapeutic interventions, aimed at modulating microRNA activity to halt or mitigate the devastating effects of ALS. Profiling microRNAs emerges as a pivotal step toward personalized medicinal approaches to treat ALS.

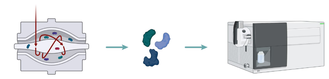


In collaboration with TEL AVIV UNIVERSITY

Biomarker Driven Proteomics

Objective: We aim to identify dysregulated ALS plasma biomarkers in 15 ALS patients vs. 15 age matched healthy controls in a discovery screen. This cassette of biomarkers will then be included in LC-MS/MS targeted proteomics assay to assess the effects of PrimeC.

Method: Discovery proteomics will be conducted using high resolution Orbitrap LC-MS/MS system, operated in DIA mode, followed by targeted proteomics assay using triple quadrupole LC-MS/MS system operated in MRM mode.



In collaboration with inoviv

Elucidating Primec MoA and Identifying Novel Biomarkers

In parallel to advancing our clinical program, the NeuroSense R&D team is working on the elucidation of PrimeC's mode of action and establishing its biological activity. This will be done using plasma from the ongoing PARADIGM study, utilizing its unique setting and constituents. NeuroSense plans to pursue the identification of new biomarkers indicative of ALS, which could in turn open a window to novel therapeutic approaches and candidates. We are currently examining the correlation between microRNA, TDP-43 and behavioral measures.

We are committed to advancing ALS research and innovation collaboratively. Our doors are always open to academic and industry partners who share our dedication to finding a cure for ALS.

Contact details: nitai@neurosense-tx.com

NeuroSense Website