**Neuroderm, Ltd.**
Sheila Oren, MD and Oron Yacoby-Zeevi, PhD, DVM (Lead PIs)

**Organization and Team Overview**

NeuroDerm is a pharmaceutical company specializing in the development of drug delivery formulations for the treatment of CNS diseases based on proprietary reformulations of well established oral drugs. NeuroDerm selected diseases where bio-availability of current therapies was identified as the major impediment to better clinical efficacy. NeuroDerm’s reformulations, when administered continuously through the skin, obtain improved kinetics and/or modes of action in the respective diseases resulting in significant – and sometimes dramatic – clinical benefit. The company focuses on CNS diseases and its leading products include novel dermal delivery for the treatment of Parkinson’s disease (PD), ADD/ADHD and other CNS disorders and diseases. NeuroDerm brings together an experienced team, notable board members and advisors. The company’s CEO, Dr. Oded Lieberman, has more than 20 years of international healthcare experience with various leading pharma and diagnostics companies; as VP in Omrix Biopharmaceuticals (NASDAQ: OMRI (acquired in 2008 by J&J), he was responsible for bringing its lead product to the market. Dr. Lieberman holds a PhD in Biology from the Hebrew University of Jerusalem and an MBA from INSEAD, France. NeuroDerm’s other team members, including Dr. Sheila Oren and Dr. Oron Yacob-Zeevi (principle investigators of the MJFF award), are all highly experienced, senior pharma industry executives, some of whom have led the development of successful new drugs (eg. Azilect for Parkinson’s Disease) and contributed significantly to the growth of their companies (eg. TEVA).

The company received investments from well known international private investors with expertise in drug development (including Mr. Robert Taub, previous founder and CEO of Omrix Biopharmaceuticals (NASDAQ: OMRI) which was wholly acquired by Johnson and Johnson in Nov. 2008), Mr. Uwe Wascher (previously of the General Electric Corp.), Mr. Juergen Hambrecht (outgoing CEO and Chairman of BASF) and Dr. Shmuel Cabilly (of the “Cabilly patent”, licensed to Genentech, on which a portion of Genentech’s revenues are based). The company was established under the aegis of Ofakim High Tech Ventures (OHV) in Israel (a wholly owned subsidiary of Capital Point, a publicly traded company in TASE) and is supported by the Office of the Chief Scientist in Israel.

**Opportunity Overview**

The company's unique technology enabled NeuroDerm to achieve a technological breakthrough and develop the first ever concentrated, stable, liquid formulation of levodopa and carbidopa (LD/CD). ND0612, NeuroDerm’s proprietary levodopa/carbidopa drug formula, is under development for continuous subcutaneous delivery through a pump patch for the treatment of PD. Unlike other current treatments, ND0612 would not require surgery, should be convenient to use, and would maintain a continuous and constant concentration of levodopa in the blood, improving the bioavailability of levodopa. It should significantly decrease motor fluctuations and possibly reverse dyskinesia. ND0612 is anticipated to provide all of the benefits of levodopa treatment with reduced motor complications; it could also have a significant clinical impact on the long-term efficacy of levodopa treatment. ND0612 is being developed as either an adjunct therapy to any oral treatment or as a mono-LD-therapy drug, and it has the potential to become a breakthrough, blockbuster PD drug. Phase I and phase IIa studies with ND0612 have been completed and showed the potential to achieve straight line LD plasma levels, both day and night, with good safety and tolerability, in a convenient administration mode (the results were presented in the *17th International Congress of Parkinson’s Disease and Movement Disorders June 2013, Sydney, Australia* – Poster(1), Poster(2)).

NeuroDerm is currently proceeding with mid-stage human clinical trials with ND0612.
Details of MJFF Grant

The Michael J. Fox Foundation for Parkinson’s Research has awarded Neuroderm a $1 million grant, for the second time, to support “A Phase 2 clinical study for the safety, tolerability and levodopa pharmacokinetics following the continuous administration of ND0612 via a pump in LEVODOPA –treated Parkinson’s disease patients with motor fluctuations.”

Results and Potential Next Steps

NeuroDerm has demonstrated the safety of the ND-0612 in a series of pre-clinical studies evaluating the effect of ND-0612 on potential systemic and local SC toxicity in pigs. NeuroDerm has also evaluated the PK profile of LD/CD and 3-OMD, the key metabolite of LD, in pigs and showed that constant therapeutic concentrations of LD were maintained following continuous SC administration of ND-0612.

Three human studies with ND-0612 administered continuously SC in healthy volunteers (Phase 1 ND0612/001, n=36 and ND0612/001b, n=18) and PD patients (Phase 2a, n=8) have been conducted. The first study of ND-0612, ND0612/001, was a Phase 1, single dose, single-center, randomized, double-blind, placebo-controlled dose escalation study evaluating safety, tolerability and LD plasma concentration following administration of SC continuously-delivered LD/CD solution (ND0612) in 36 healthy volunteers. Conclusion: results of study ND0612/001 in 36 healthy volunteers showed that ND0612 administered SC for 24h continuously was safe and tolerated for ND0612. LD plasma levels increased linearly with the ND0612 dose (infusion rate).

Following a DMC approval, a Phase 1b continuation of Study NC0612/001 was conducted in an additional eighteen (18) healthy male volunteers. Conclusion: ND0612 reached steady, clinically significant, dose-related LD plasma concentrations. ND0612 showed good tolerability and safety. Local response was minor, typical to other continuously administered SC drugs (e.g. insulin). A Phase 2a clinical investigation was conducted to determine the steady state (SS) plasma concentrations of LD and CD following SC delivery of ND0612, LD PK profile following oral LD/CD with and without ND0612, as well as safety and tolerability of ND0612 versus saline in PD patients for 24 hours. Conclusion: Preliminary data from 8 advanced Parkinson’s disease patients showed that subcutaneous ND0612 delivery achieved steady-state plasma LD concentrations ranging from 700-900 ng/ml (which is a typical therapeutic range). Fluctuations in LD plasma concentration were significantly reduced. With ND0612, LD concentration could be adjusted by controlling the infusion rate (programmed during day and night) and by adding oral LD/CD and a COMT inhibitor. Peripheral catechol-O-methyl transferase (COMT) was probably the main metabolic pathway acting on LD. The amount of entacapone provided in Stalevo® was apparently insufficient to inhibit the extensive COMT activity. Therefore, we conclude that, with ND0612, additional inhibition of COMT would further contribute to increasing plasma LD concentration. With minimal oral doses, LD plasma concentrations should exceed >1500 ng/ml with very low peak:trough ratio.

Clinical study Conclusions:

- ND0612 reached steady, clinically significant, dose related LD plasma concentrations
- ND0612 showed good tolerability and safety
- Local response was minor, typical to other continuously administered SC drugs (e.g. insulin).

ND0612 will undergo a full Clinical Development Plan (CDP).

ND0612 is expected to be tested in a clinical study of repeat dose, oral dosing adjustment & dosing management in 2013, and in Phase II-III Pivotal Studies under IND in 2014.

By overcoming the short half life of orally administered L-DOPA, the company thus hopes to minimize or even reverse some of the disabling late motor complications associated with current L-DOPA oral administration. Moreover, by providing newly diagnosed patients with low, continuous levels of L-DOPA the company hopes to be able to prevent or significantly delay the later emergence of dyskinesia and other late stage motor complications.

NeuroDerm intends to enter into collaboration and/or licensing agreements for the development and/or marketing of its products with major pharmaceutical or medical devices companies. The primary objective of these collaborations is to ensure that the company’s intended premium products will be supported by robust marketing and sales efforts of a major pharma market leader in the specific disease area.

Intellectual Property Status

The company’s core technology and formulations are protected by strong international, wide-scope issued patents, and newer pending patent applications.

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