CLE-400
a novel non-opioid topical treatment for painful diabetic neuropathy

Dr. Orna Goren
Products Cluster Leader, Clexio

SMi conference May 11th, 2021
Disclaimer

This presentation has been prepared by Clexio Biosciences Ltd. (the "Company") and is general background information about the Company’s activities at the date of this presentation. The information in this presentation is provided in summary form only and does not purport to be complete. This presentation does not contain all the information that is or may be material to investors/collaborators or potential investors/collaborators and should not be considered as advice or a recommendation to investors/collaborators or potential investors/collaborators. By attending the presentation or by reading the presentation slides you agree to be bound as follows: This presentation has been made to you solely for information purposes. This presentation may be amended and supplemented as the Company sees fit, may not be relied upon for the purpose of entering into any transaction and shall not be regarded as a recommendation in relation to any such transaction whatsoever. This presentation and its contents are proprietary to the Company, and no part of it or its subject matter may be reproduced, redistributed, passed on, or the contents otherwise divulged, directly or indirectly, to any other person (excluding the relevant person’s professional advisers) or published in whole or in part for any purpose without the prior written consent of the Company. If this presentation has been received in error it must be returned immediately to the Company. This presentation contains forward-looking statements. These statements may include the words “believe”, “expect”, “anticipate”, “intend”, “plan”, “estimate”, “project”, “will”, “may”, “targeting” and similar expressions as well as statements other than statements of historical facts including, without limitation, those regarding business strategy, plans, targets and objectives of the management of the Company for future operations (including development plans and objectives). Such forward-looking statements involve known and unknown risks, uncertainties and other important factors which may affect the Company’s ability to implement and achieve the budgetary plans, fiscal guidelines and other development benchmarks set out in such forward-looking statements and which may cause actual results, performance or achievements to be materially different from future results, performance or achievements expressed or implied by such forward-looking statements. Such forward-looking statements are based on numerous assumptions regarding the Company’s present and future plans and the environment in which the Company will operate in the future. Furthermore, certain forward-looking statements are based on assumptions or future events which may not prove to be accurate, and no reliance whatsoever should be placed on any forward-looking statements in this presentation. The forward-looking statements in this presentation speak only as of the date of this presentation, and the Company expressly disclaims to the fullest extent permitted by law any obligation or undertaking to disseminate any updates or revisions to any forward-looking statements contained herein to reflect any change in expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based. Nothing in the foregoing is intended to or shall exclude any liability for, or remedy in respect of, fraudulent misrepresentation. The information in this presentation has not been independently verified. No representation or warranty, express or implied, is made as to the fairness, accuracy or completeness of the presentation and the information contained herein and no reliance should be placed on it. Information in this presentation (including market data and statistical information) has been obtained from various sources (including third party sources) and the Company does not guarantee the accuracy or completeness of such information. All projections, valuations and statistical analyses are provided for information purposes only. They may be based on subjective assessments and assumptions and may use one among alternative methodologies that produce different results and to the extent they are based on historical information, any they should not be relied upon as an accurate prediction of future performance. Any financial data in this presentation are solely for your information, as background to the Company and may not be relied upon for the purpose of entering into any transaction whatsoever. Furthermore, no representation is made as to the reasonableness of the assumptions made in this presentation or the accuracy or completeness of any modelling, scenario analysis or back-testing. The information in this presentation is not intended to predict actual results and no assurances are given with respect thereto. None of the Company, its advisers, connected persons or any other person accepts any liability whatsoever for any loss howsoever arising, directly or indirectly, from this presentation or its contents. All information, opinions and estimates contained herein are given as of the date hereof and are subject to change without notice.
A clinical stage company redesigning therapies for **neurological** and **psychiatric** conditions
Clexio at a glance

Multi-asset pipeline
✓ Lead asset in Phase 2
✓ Additional assets in Phase 1
✓ Preclinical pipeline

Focus on Psychiatry and Neurology
✓ Targeting significant unmet needs and growing markets

Technological and therapeutic innovation
✓ 27 patent families, 12 granted in US
✓ Proprietary technologies
✓ Internal pipeline creation capabilities
## Clexio’s pipeline

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>PRE CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLE-100</td>
<td>Major Depressive Disorder</td>
<td>Depression in Bipolar Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDA receptor antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLE-400</td>
<td>Chronic Pruritus (initial focus on itch of neurological origin)</td>
<td>Painful Diabetic Neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potent α2-adrenergic (and SST4, and H4) receptors agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLE-500</td>
<td>Cluster Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG block</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLE-600</td>
<td>Parkinson’s Disease (enabled by OLAR®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine precursor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CLE-400

A novel non-opioid topical treatment under development for painful diabetic neuropathy and chronic pruritus

CLE-400 is a new investigational drug that has not been approved for commercial distribution.
**CLE-400 novel topical agent for high unmet need**

### Painful Diabetic Neuropathy

2.6 million patients in the US suffer from Painful Diabetic Neuropathy (PDN)\(^1\)

Less than **50% of patients** achieve significant benefit with any single drug \(^2\)

*Topical treatment is highly desirable for PDN patients who suffer from multiple co-morbidities*

### Chronic Pruritus

23-44 million patients in the US suffer from chronic pruritus due to cutaneous or systemic conditions \(^3\)

No FDA approved treatment

**Pathophysiological types:**
- Dermatological
- Systemic
- Neuropathic (e.g. BRP, NP, Post-burn)

Safe and efficacious treatment options are limited for Peripheral Neuropathic conditions (both pain and itch).

---

1. Painful Diabetic Neuropathy - Global Drug Forecast and Market Analysis to 2026: GDHC164PIOR Published: 1.2018
2. Freynhagen R, Bennett MJ. Diagnosis and management of neuropathic pain. BMJ. 2009 Aug 12;339:b3002
3. Molanazar, Nicholas K., Savannah Dean Koch, and Gil Yosipovitch. “Epidemiology of chronic pruritus: where have we been and where are we going?.” Current Dermatology Reports 4.1 (2015): 20-29
CLE-400 a Novel, Non-Opioid Topical Treatment for PDN

A New Molecule for PDN
- Detomidine, a potent $\alpha_2$-adrenergic receptor agonist activating additional potentially therapeutically relevant targets (SST4R, H4R)
- Approved as a systemic medication for veterinary use. Never developed for human.

Targeting $\alpha_2$-adrenergic receptors peripherally
- Systemically administered $\alpha_2$-adrenoceptor agonists are used in pain management and anesthesia. Their use is limited to invasive RoA and may lead to systemic AEs
- Clexio’s Immunohistochemistry studies demonstrated that $\alpha_2$-ARs, H4R and SST4R are expressed in the skin
- Activation of these receptors could produce analgesia by inhibiting the excitability and neural signaling from the peripheral nociceptors (C-fibers) to the brain

The technology
- CLE-400 gel formulation was developed to deliver high dermal concentrations over extended period of time [depot effect in the skin] while maintaining limited systemic exposure
CLE-400 – highlights on development

**A potent α2-adrenoceptor agonist**
activating additional relevant targets (SST4R, H4R)

**Peripheral effect**
Targeting peripheral nociceptors, limiting systemic exposure

**Long lasting effect**
depot effect in the skin, once daily administration

**Significant effect demonstrated in two Pain pharmacological models:**
- Onset within 1hr of treatment (PNT)
- Cumulative analgesic effect

**Significant effect demonstrated in pre-clinical Pruritus pharmacological model:**
- Significantly suppressed chloroquine-induced scratching behaviors

**Completed successfully FIH SAD study, 3 doses tested**
- Dose linearity
- PK: suitable for QD administration
- Safety supports proceeding to MAD with all doses

**Starting MAD, preparing Ph2 in neuropathic itch and in PDN**
Proposed Mechanism of Action
Potential Multi-Modal MOA of Detomidine

**α2A adrenoceptor agonist**
(EC₅₀ ~24 nM)
- The systemic analgesic effect of another α2 adrenoceptor agonist (clonidine) has been demonstrated in pain.
- α2 adrenoceptors have been shown to be expressed on nociceptors in skin epidermis \(^{[1]}\).
- Topical administration of α2 adrenoceptor agonist may inhibit abnormal nociceptor excitability associated with pain.

**Histamine H4R agonist**
(EC₅₀ ~5 µM)
- H4 receptor is expressed in immune cells, dermal fibroblasts and keratinocytes, CNS, DRG and in peripheral afferent nerve fibers.
- Systemic administration of H4 receptor agonists has been shown to alleviate painful peripheral neuropathy in multiple rodents models \(^{[2]}\).

**Somatostatin SST4R agonist**
(EC₅₀ ~7 µM)
- SST4 receptors are localized in the CNS, peripheral immune cells, DRG and skin epidermis.
- Systemic administration of SST4 agonists exhibited analgesic effects in various rodent pain models, including inflammatory pain, back pain, cancer pain and neuropathic pain \(^{[3]}\).

---

2. Sanna et al, Pain, 2015 Dec;156(12):2492-2504
α2A-Adrenergic Receptor expression in the skin of Peripheral Neuritis Trauma (PNT) pigs

Legend: N - nerve, BV - blood vessel, Epi - epidermis, HF - hair follicles

Clexio confirmed α2A expression in pig skin (epidermis, dermal nerves, blood vessels and hair follicles) using immunohistochemistry staining, supporting the hypothesis of CLE-400 peripheral activity
Clexio evaluation of CLE-400 in relevant Pain preclinical models

- Peripheral Neuritis Trauma (PNT)
- Post Operative Pain (POP)
Peripheral Neuropathic Pain Pig Model

Peripheral neuritis trauma (PNT) model was developed in domestic pigs* to understand the pathophysiology of chronic neuropathic pain.

Pig is considered an excellent model for topical application due to their skin resemblance to humans skin and potential better clinical translation than rodents.

Gabapentin and Morphine have shown efficacy in this model (inhibited evoked and spontaneous pain).

PNT in pigs serves as a valid preclinical model for the study of the chronification of peripheral nerve injury and for investigation of new pain therapies.

Induction of Neuropathic Pain

Animals are anaesthetized and an incision is made through the skin and fascia on the left side of the lower back, approximately 1 cm lateral and parallel to the spine line of the pig. The muscles are then retracted, and the sciatic nerve exposed.

Following sciatic nerve exposure, PNT is induced by silk threads, immersed in complete Freund's adjuvant overnight to induce inflammation. The threads are used to create 3 loose ligations surrounding the lateral half of the sciatic nerve bundle.

2 weeks after surgery, once chronic neuropathic pain is established, CLE-400 was topically applied twice daily for 2 weeks on the outer area of the leg that is innervated by the injured sciatic nerve.
The analgesic activity of CLE-400 at 3 doses administered topically (BID) for 14 days was evaluated on PNT-induced neuropathic pain in pigs. Von Frey (VF) assessment was used to evaluate mechanical sensitivity. A lower withdrawal force threshold indicates severe pain.

Mean (± SEM) group withdrawal response (g) following von Frey stimulation:

- *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001 CLE-400 1% vs. placebo using one-way Anova followed by Tukey test
- *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001 Gabapentin vs. placebo using one-way Anova followed by Tukey test

CLE-400 exhibited a dose-dependent analgesic effect as early as 1hr. Repeated dosing enhanced the analgesic effect.
Topical administration of CLE-400 twice daily for 14 days exhibited a **dose-dependent** analgesic effect, with CLE-400 1% alleviating pain in a **statistically significant** manner as soon as 1 hr after the first treatment.

Cumulative analgesic effect with repeated administrations of CLE-400.

Effect is achieved when gel is applied on the dermatome and not on lesion area itself.

No motor impairment/sedation were observed (tested in open field apparatus)
Acute Post-Operative Pain (POP) Model
Acute Post-Operative Pain (POP) Pig Model

A validated model of POP in pigs was used to assess the topical analgesic effects of CLE-400.

The pig model of incisional pain provides greater translational relevance for validating new topical and localized pain treatments in humans* as pigs skin bares notable similarity to human anatomy.

The anesthetized animals are undergoing a 6-7 cm long skin and fascia incision in the left flank, keeping the muscle intact. The skin incision is then closed using a sterile suture.

CLE-400 was applied twice daily for 6 days (Day 0 to Day 5) starting 15 min following surgery on Day 0, on the skin area surrounding the incision (left flank).

Analgesic effects of CLE-400 (0.1 to 1.0%) post-surgery were evaluated on Days 0-5 by measuring withdrawal threshold to von Frey filaments (as a measure of pain).

**CLE-400 results in pig POP model – Mechanical Sensitivity**

(measured by Von Frey assessment)

![Graph showing mean withdrawal force (g) following von Frey stimulation for different groups.

**Mean (± SEM) group withdrawal response (g) following von Frey stimulation:**

*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001 vs. placebo using one-way Anova followed by Tukey test. Von Frey assessment on D1-D5 was performed 1 hour post morning application of CLE-400

Topical application of CLE-400 0.33% for 6 days resulted in statistically significant increase in pain threshold as soon as Day 1 (2nd day of treatment) and this effect increased gradually up to Day 5
Following the procedure, placebo-treated pigs developed high sensitivity to mechanical stimulation, detectable spontaneous behavioral changes and had minor to nonexistent motor dysfunction, demonstrating validity of the model.

Twice daily topical application of CLE-400 0.33% for 6 days resulted in statistically significant analgesic effects as soon as Day 1 (Day 0 is defined as the 1st dosing day) and this effect increased gradually up to Day 5, indicative of a cumulative effect with repeated dosing.

The total walking distance in the open field apparatus was not affected by CLE-400 at any dose level, suggesting that no motor impairment/sedation were observed.
Phase 1 studies
CLE-400 Phase 1 studies - SAD

Single Ascending Dose (SAD) study completed successfully (Germany, Oct 2020)

Study design
- A Placebo-controlled, Randomized, Double-blind Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of Single Escalating Topical doses of CLE-400 (3 strengths) in Healthy Subjects
- 10 subjects per cohort (total of 30 subjects): 8 subjects received CLE-400, 2 received placebo on Day 1, followed up to 8 days after dosing

Safety
- All 3 cohorts were completed successfully
- The safety results support proceeding with clinical development

PK
- Dose proportionality was demonstrated
- PK profile supportive of once daily administration
CLE-400 ongoing studies and next steps

• **Ongoing Multiple Ascending Dose (MAD) study:**
  A Placebo-controlled, Randomized, Double-blind Phase 1 Study to Assess Safety, Tolerability, and Pharmacokinetics of Multiple Escalating Topical Doses of CLE-400 applied once daily in Healthy Subjects

• **Preparing for Ph2 POC studies in PDN and in Neuropathic itch**
Thank you

Dr. Orna Goren, Products Cluster Leader, Clexio
Orna.Goren@Clexio.com