CLX-117

CLX-117: A NOVEL SALT OF BUPIVACAINE FOR THE MANAGEMENT OF PAIN INDUCED BY ORAL MUCOSITIS IN HEAD AND NECK CANCER PATIENTS UNDERGOING CHEMO/ RADIOTHERAPY

- ✓ Bupivacaine HCl is an approved drug indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures, subarachnoid block (spinal anesthesia).
- ✓ CLX-117 portfolio includes:
    - A novel salt of bupivacaine gamma linolenic acid
    - A novel salt of bupivacaine linolenic acid
    - A novel salt of bupivacaine lauric acid
- ✓ Designed to undergo simple dissociation into active moieties (bupivacaine and fatty acids which are GRAS listed/available as essential fatty acids) in saliva of oral mucositis patients
- ✓ The dissociated bupivacaine and linoleic acid/gamma linolenic acid have beneficial pharmacological effects
- ✓ Bupivacaine exerts its action as local anesthetic, sustained for longer period of time; FA will have anti-inflammatory and anti-microbial effect in oral mucositis.
- ✓ Pilot *in vitro* study had shown dissociation of bupivacaine moiety comparable to that of bupivacaine hydrochloride.
- ✓ Intellectual Property: US Patent Pending

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1. OPPORTUNITY OVERVIEW

CLX-117 is a portfolio of compounds includes novel salts of bupivacaine with gamma linolenic acid, linoleic acid and lauric acid delivering local anesthesia with potential antibacterial and antifungal effect. These novel salts are designed to undergo simple dissociation into active moiety in saliva of oral mucositis patients. CLX-117 is expected to have a significantly improved delivery of the drug for the production of local analgesia along with its added benefit on controlling infection in oral mucositis patients.

Oral mucositis represents a major non-hematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity; pain, odynodysphagia, dysgeusia, and subsequent dehydration, malnutrition and reduced quality of life of affected patients. In addition, oral mucositis represents a significant risk factor for local or systemic infections, particularly in neutropenic patients. Thus, oral mucositis is a highly significant makes the patient less likely to comply with their cancer treatment, increases mortality and morbidity and contributes to rising health care costs (Piatkowska-Jakubas B *et al*., 2003, Lalla R.V. et al., 2008 and Laheij *et al* 2012).

In head and neck radiotherapy where the doses were greater than 5,000 cGy and in stem cell transplants, the incidence rate was 100% and almost 90%, respectively (Cawley MM and Benson LM, 2005). Bone marrow-suppressing (myeloablative) chemotherapy is associated with a mucositis risk of 60 to 100%, while the chemotherapy and radiotherapy reveals a risk of almost 100% (Carlos Alvariño-Martín *et al*., 2014).

Infections in oral mucositis:

Colonization by bacteria, fungi, and viruses tend to occur mainly at the ulceration phase and superimpose secondary infections in the damaged mucosa (Vanhoecke B *et al*, 2015). The most common infection in the oral cavity during or shortly after radiotherapy and chemotherapy is

Candidosis, many patients become colonized intra-orally with *Candida albicans* during cancer therapy.

The prevalence of positive Candida cultures increased from 43% at baseline to 62% at completion of cancer therapy and to 75% during the follow up period (Vanhoecke B *et al*, 2015, Ramirez-Amador V *et al*., 1997 and Jham B.C. *et al*., 2006). The systematic review carried out by Napenas *et al*, 2007 showed that the most frequent Gram-negative species isolated in patients with oral mucositis associated during chemotherapy were from the *Enterobacteriaceae* family, *Pseudomonas* sp. and *E. coli*.

The most common Gram-positive species isolated were *Staphylococcus sp. And Streptococcus sp (Napenas et al., 2007*). In HSCT, the presence of the Gram-negative *Porphyromonas gingivalis* in oral rinsing samples was positive predictive factor for developing oral ulcerations (Laheij *et al*, 2012). The oral pain associated with the lesion frequently leads to the need for enteral nutritional support with or without use of a feeding tube or gastrostomy, as well as use of opioids. Microorganisms are generally believed to intensify the inflammatory process and aggravate or promote the formation of ulcers. Hence there is a clear unmet need in the management of oral mucositis in controlling inflammation and associated infection.

CLX-107 portfolio contains novel salt of bupivacaine and fatty acid (GRAS listed), which offer a unique profile of induction of pain relief as well as controlling of infection in the oral mucositis associated with chemo/radiotherapy.

2. UNMET MEDICAL NEED

Cytotoxic chemo/radiotherapy therapy has long been associated with a high risk of oral mucositis. Oral toxicities have a tremendous impact on the cancer patient and on the resources of the healthcare system. Oral mucositis can be very painful and can significantly affect nutritional intake, mouth care, quality of life and cause of dose delays and interruptions of cancer therapy. Unfortunately, the currently available treatments for oral mucositis are only palliative and

marginally effective. The lack of effective treatment options and prevention strategies could also have attributed to the fact that research on oral toxicities has lagged behind research on other chemotherapy and radiation-related toxicities such as febrile neutropenia and nausea and vomiting. In addition, infection associates the oral mucositis especially in the patients with Grade III or IV, often there is additional requirement of controlling local or systemic infection. Microorganisms are generally believed to intensify the inflammatory process and aggravate the formation of ulcers. Emphasizing good oral hygiene practices to patients is important to reduce the chances of developing infection secondary to mucositis. Fungal and bacterial infections are common with these lesions and antifungal and/or antibacterial medications may be prescribed as needed.

Hence there is a clear unmet need for a convenient therapy which could offer potential benefit in the management of oral mucositis in controlling pain, inflammation and associated infection.

3. SCIENTIFIC RATIONALE

Bupivacaine hydrochloride is related chemically and pharmacologically to the aminoacyl local anesthetic, with a well-established long acting effect and is currently available on the market for other indications as an injectable drug product. It is a homologue of mepivacaine and is chemically related to lidocaine. Bupivacaine is an approved drug indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures, subarachnoid block (spinal anesthesia). It is a potent agent with a slow onset, but despite this, is a popular choice due to its prolonged duration of action. It block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse by reducing the rate of rise of the action potential (McLure H.A and Rubin A.P., 2005).

Linoleic acid is a poly-unsaturated omega-6 fatty acid and GRAS listed long chain fatty acid. It is an essential fatty acid in mammalian nutrition and involved in the biosynthesis of

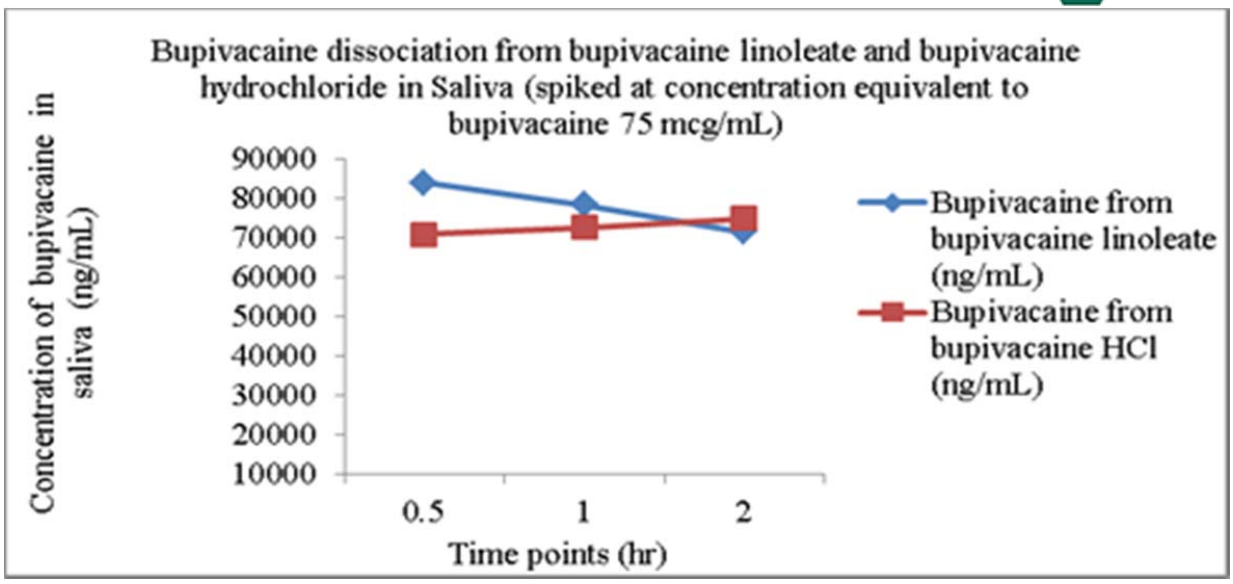
prostaglandins and cell membranes. Linoleic acid reported to have anti-microbial activity at 25 mcg/ml against *Actinobacillus actinomycetemcomitants*, *Fusobacterium nucleatum*, *Streptococcus mutans, Streptococcus gordonii, and Streptococcus sangius* (Huang C.B. et al., 2010). The n-6 fatty acids, (LA) were bactericidal at a concentration of 25µg/mL. The minimum inhibitory concentration for linoleic acid against *Porphyromonas gingivalis* was 78 mcg/ml (Choi *et al*., 2013). Similarly, Gamma linolenic acid also has been reported to have antibacterial effect in various *in vitro* studies.

CLX-117 is novel salt of bupivacaine with fatty acids, which possess following characteristics

- Designed for simple dissociation into bupivacaine and fatty acid molecules (which are GRAS listed and essential fatty acid)
- The dissociated bupivacaine and linoleic acid/gamma linolenic acid have beneficial pharmacological effects
- Bupivacaine exerts its action as local anesthetic, sustained for longer period of time; FA will have anti-inflammatory and anti-microbial effect.
- Pilot *in vitro* study had shown dissociation of bupivacaine moiety comparable to that of bupivacaine hydrochloride.
- Robust patent estate

4. ***In vitro* DATA:**

The *in vitro* dissociation study data suggest that CLX-SYN-G24-C03 and Bupivacaine hydrochloride or Linoleic acid exhibited no difference in the calculated Bupivacaine or Linoleic acid in saliva samples at the end of incubation, after the compounds were spiked in the saliva (at the concentration equivalent to 75 mcg of Bupivacaine /mL or 75 mcg of Linoleic acid /mL in saliva).



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