OncoZenge

The case for BupiZenge™

Addressing critical unmet needs for safe and effective, non-opioid pain relief in cancer care

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2. Executive Summary

Oral mucositis is a common, devasting side effect of cytotoxic chemotherapy and radiation therapy used for most forms of cancer. Deep, diffuse ulcers develop throughout the mouth. The dominant symptom of oral mucositis is pain that can be of such severity that it impairs patients' ability to continue with optimal cancer treatment, limits normal eating to the extent that parenteral nutrition is required, and can be the cause of unplanned emergency room visits and hospitalizations. Severe oral mucositis is an important reason for dose de-escalation of anti-cancer drugs and radiation treatment interruptions, both of which impair the effectiveness of cancer therapy and can worsen survival outcomes. Oral mucositis-related pain can reach a level of severity that makes eating a solid diet impossible. It occurs with a frequency of 40% to 90% in patients receiving cancer treatment, with the highest prevalence among those patients receiving radiation treatment for head and neck cancers.

There is no specific treatment for the prevention or treatment of oral mucositis or oral mucositis-related pain currently approved in the EU. The current cornerstone for the management of pain related to oral mucositis is symptom control, which is heavily dependent on the use of systemic opioids. Not only do the side effects of these drugs often impair patients' cognitive function, but they are also associated with a broad range of symptoms that affect patients' ability to function normally and may cause dependence. There is a large unmet medical need for a treatment that effectively and safely mitigates oral mucositis pain.

BupiZenge™ addresses this unmet need as it effectively alleviates local oral mucositis pain, has a good safety and tolerability profile, is not based on opioids, and is being developed as a treatment tailored to patients who suffer from different levels of oral mucositis pain. BupiZenge™ is an oral, slow-release, dissolvable lozenge that delivers bupivacaine, a non-opioid based topical anaesthetic, directly to the oral mucosa and is being developed to manage the pain associated with oral mucositis for up to 6 weeks in oncology patients undergoing radiation and/or chemotherapy. While the topical formulation provides excellent targeted analgesic effects, it does so without resulting in significant systemic uptake or dependency. Bupivicaine is a well-known anaesthetic agent shown to be effective and safe in other indications.

There is strong urgency of making a specific treatment available for patients affected by oral mucositis pain as these individuals lack safe, reliable, well-tolerated and effective therapeutic options despite decades of research. BupiZenge™ is being developed to provide targeted pain mitigation with a topical administration (resulting in low systemic levels and toxicity concerns) as a precision medicine treatment to be used only by those patients who need it and when they need it.

Significant positive results indicative of safety and clinically meaningful efficacy in Phase 1 and Phase 2 trials strongly suggest that BupiZenge™ could fill a critical gap in the management of oral mucositis pain in cancer patients. Such an outcome is strongly aligned with the EU Cancer Mission's Quality of Life objectives.

OncoZenge is currently planning a pivotal Phase 3 program to bring BupiZenge™ to market together with a partner.

3. Background information on the disease

3.1. Oral Mucositis ("OM")

Oral mucositis ("OM") is a severely debilitating condition characterized by painful erythema, oedema, and deep, diffuse ulcerations of the oral mucosa. Severe pain is the most consistent symptom of OM and is often refractory to aggressive systemic analgesia. Oral mucositis is among the most common and clinically significant side effect of cytotoxic anti-cancer treatments (Lalla et al. 2019). OM is consistently cited by patients as one of the most impactful side effects of their treatment. Patients treated with standard regimens of concomitant chemoradiation (CRT) for cancers of the oral cavity (OC) or oropharynx (OPC) are especially vulnerable. Of approximately 100,000 patients with newly diagnosed OC or OPC in Europe this year, the majority with locally advanced disease will be treated with CRT, and of these individuals, virtually 100% will develop ulcerative lesions of their oral mucosa and almost three-quarters will develop OM-induced pain of such severity as to prohibit the ingestion of a solid diet and a dependence on opioids for symptom management.

Critically, the significance of OM extends far beyond patients' pain or its deleterious impact on quality of life. OM is among the most common reasons for the treatment interruptions. **Among patients treated with radiation therapy for head and neck cancer (HNC), treatment breaks are reported to be almost four times more common in patients with ulcerative OM (Russo et al. 2008) than in patients without the condition. Mucositis in patients being treated with CRT doubles the risk of a reduction in treatment intensity (Rosenthal 2007). The consequence on tumour response is marked. In a recent study of 37,314 head and neck cancer patients, even short breaks of 2-8 days resulted in a significant reduction in 5-year overall survival (65% to 58%, p<0.001).** For longer breaks (>8 days), the results were even more profound (overall survival 45%) (Xiang et al. 2020). Prolongation of radiation therapy increased the relative hazard of death by 2% per day (p<0.0001, Xiang et al. 2021).

And while OM drastically impacts patients' tolerance of cancer therapy, it also creates an untoward burden of overall cost and healthcare resource use. **A recent healthcare claims-based analysis reported that the incremental cost of OM in HNC patients being treated with radiation therapy was more than USD $30,000 (Hoffbauer et al. 2020), almost twice the amount reported by Nonzee and colleagues a decade earlier (Nonzee et al. 2008).** Increasing OM severity is associated with increased resource use and healthcare expenditure such as for nutritional supplementation (gastrostomy and tube feeding dependence), and hospitalization (Vera-Llonch et al. 2006). Currently, 35% of HNC patients receiving CRT (typically delivered in an ambulatory setting) are hospitalized with increasing lengths of stay (6.6 days) at an average cost of over USD $18,000 (Boakye et al. 2019).

Unplanned hospitalizations or Emergency Department visits are more common among HNC patients whose treatment regimen is most closely linked to OM risk. Whereas the rate of unplanned hospitalizations or emergency department visits has been reported as 0.50 per 100 patient-days for individuals receiving radiation therapy only, and 0.55 if surgery is included in the regimen; it rises to 0.86 for patients receiving CRT, which is strongly linked to developing OM (Eskander et al. 2018). Because of a shift in recent decade of HNC aetiology to one dominated by human papillomavirus (HPV) as the causative agent, primary tumour locations tend to be in the posterior oral cavity.

Consequently, the soft palate is most often impacted in cases of OM, a site at which OM even more dramatically impairs function. This is reflected in the fact that 63% of HPV-positive OPC patients become dependent on a gastrostomy tube for feeding (Setton et al. 2015). It is clear that OM, aside from its overwhelming symptom burden and detrimental consequences on quality of life and well-being, is a significant impediment to optimal anti-cancer therapy and poses a significant burden of healthcare expenditure and resource use.

3.2. Epidemiology and clinical characteristics

Oral mucositis associated with chemotherapy

Oral mucositis is a significant and common side effect of cancer treatments that are either based on chemotherapy or radiation therapy. While the overall pathogenesis is similar, the incidence, severity and course of the condition is not. Clinically meaningful symptomatic OM occurs in about 40% of patients who receive common cycled regimens of chemotherapy and in patients getting conditioning tregimens prior to hematopoietic stem cell transplants (Al-Ansari et al. 2015). Chemotherapy-associated OM typically occurs within 4-5 days following chemotherapy infusion and is characterized by erythema of some or all of the mucosa of the mouth (Villa & Sonis 2016). While some patients' OM will not progress beyond atrophy and erythema, for many, epithelial integrity is breached by day 7 and characterized with the formation of exquisitely painful, deepening and expanding ulcers with peak destruction apparent by days 10-14 – precisely coinciding with the patient's white cell nadir during the chemotherapy cycle (Ruescher et al. 1998). Ulcers may present with a surface pseudomembrane comprised of necrotic tissues and elements of the oral microbiome (Figures 1 and 2). Ulcers persist for about a week and then, in most cases, spontaneously resolve by day 21. The same course characterizes mucositis with each chemotherapy cycle. In the absence of chemotherapy dose de-escalation, mucositis risk increases with cycles after the one during which OM first manifest.

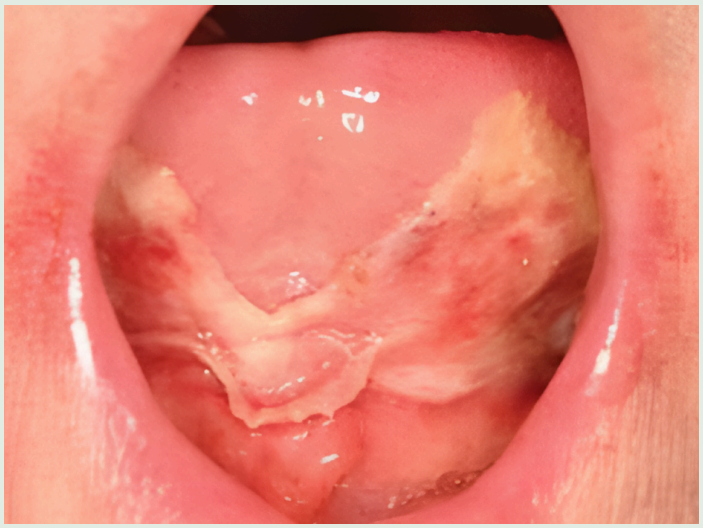


Figure 1. *Severe oral mucositis in a patient receiving chemotherapy.*

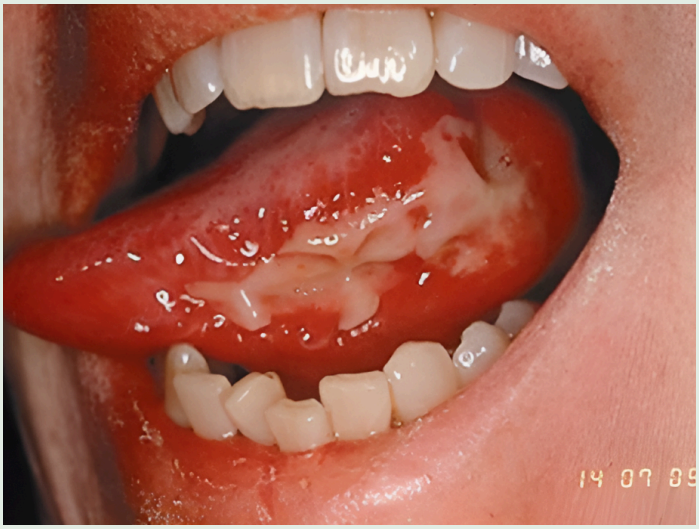


Figure 2. *Severe OM associated with radiation therapy for treatment of oral cancer.*

Oral mucositis associated with radiotherapy with or without concomitant chemotherapy

Virtually every patient who receives radiation therapy in which the fields encompass any part of the oral cavity and/or oropharynx is at high risk of developing significant OM. Indeed, more than two-thirds of this patient cohort will have OM of such severity as to result in either a diet that is liquid-based, or not be able to take any sustenance by mouth. OM associated with radiotherapy has a more gradual onset with a prolonged course (Figure 3, Sonis 2009). While concomitant chemotherapy is associated with a higher risk of severe mucositis compared to radiation only, its use is associated with better survival (DeFelice et al. 2021). Reliance on opioid-based pain management and shifts to non-solid diets commonly follow the course of ulcer development with progressively more intense radiation therapy, as do undesirable treatment interruption because of the patient's OM symptoms. The ulcers that typify OM are irregular, deep, and often covered by a pseudomembrane and usually last for two to four weeks following the last day of radiation, although in about 5% of cases the duration may extend well beyond that time. Figure 2 summarises the usual course of OM during radiation therapy.

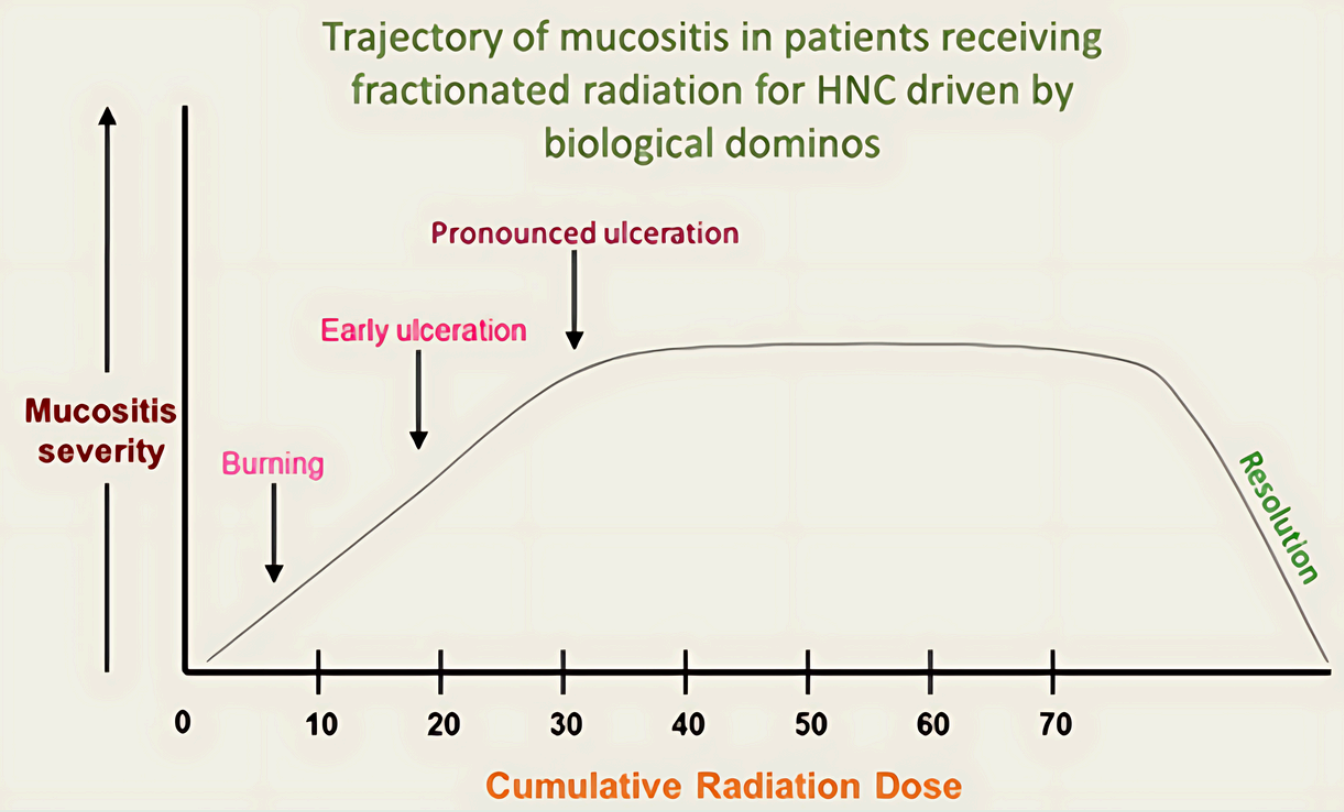


Figure 3. *Trajectory of OM in HNC patients treated with radiation therapy.*

OM distribution is impacted by the radiation fields. While the majority of HNC patients are treated using intensity modulated radiation therapy, typically, more than one oral mucosal surface is impacted (Sonis et al. 2004). Similar to chemotherapy-associated OM, radiation therapy-associated OM is overwhelmingly associated with the movable mucosa. OM of the soft palate, ventral tongue and floor of the mouth appears to be most impairing for patients. (Figure 2).

3.3. Risk of severe oral mucositis

OM risk is not uniform across patients undergoing cancer treatment (Sonis 2013). Among patients treated with concomitant chemoradiation, about 65-70% will develop severe OM. The incidence is similar for patients in which total body radiation is a component of their hematopoietic stem cell conditioning regimen, but lower (about 35-40%) for patients treated with chemotherapy (Warhill et al. 2020). OM risk is determined by four factors: treatment components and intensity, patient-related factors, tumour-related elements, and the local oral environment (Sonis 2009). Dose-dense chemotherapy protocols and high-intensity head and neck radiation, as well as combinations of chemotherapy with radiation are associated with increased risk of severe OM. It is currently difficult to predict which patients will develop severe OM. Thus, having an effective topical therapeutic option specific for the pain associated with OM that can be applied to a wide range of patients is highly desirable. The BupiZenge™ approach is targeted and specific for those patients whose "pain trajectory" indicates highest risk of severe OM and hence allows intervention to prevent progression to more severe pain and the bad outcomes associated with it.

3.4. Pathogenesis

The pathogenesis of OM is complex. Direct DNA damage to epithelial clonogenic stem cells can results in their demise with consequent loss of renewal, tissue atrophy and then ulceration. This clonogenic cell death account for about 30% of basal cell injury (Elad et al. 2020). Initiation of OM is characterized by limited direct clonogenic cell death, generation of reactive oxygen species and activation of the innate immune response. Pathway signalling ensues resulting in activation of several transcription factors and the production of pro-inflammatory cytokines. Simultaneously, lipid peroxidation and activation of matrix metalloproteinases accelerates epithelial injury and damage to the connectives (Peterson et al. 2016). In the next phase, ulceration occurs. Deep, broad, painful ulcers are typically colonized by the local microbiota. The final phase of OM, healing, occurs spontaneously and is characterized by signalling and crosstalk between cells in the submucosa and epithelium which direct epithelial proliferation and differentiation (Zecha et al. 2019, Figure 4).

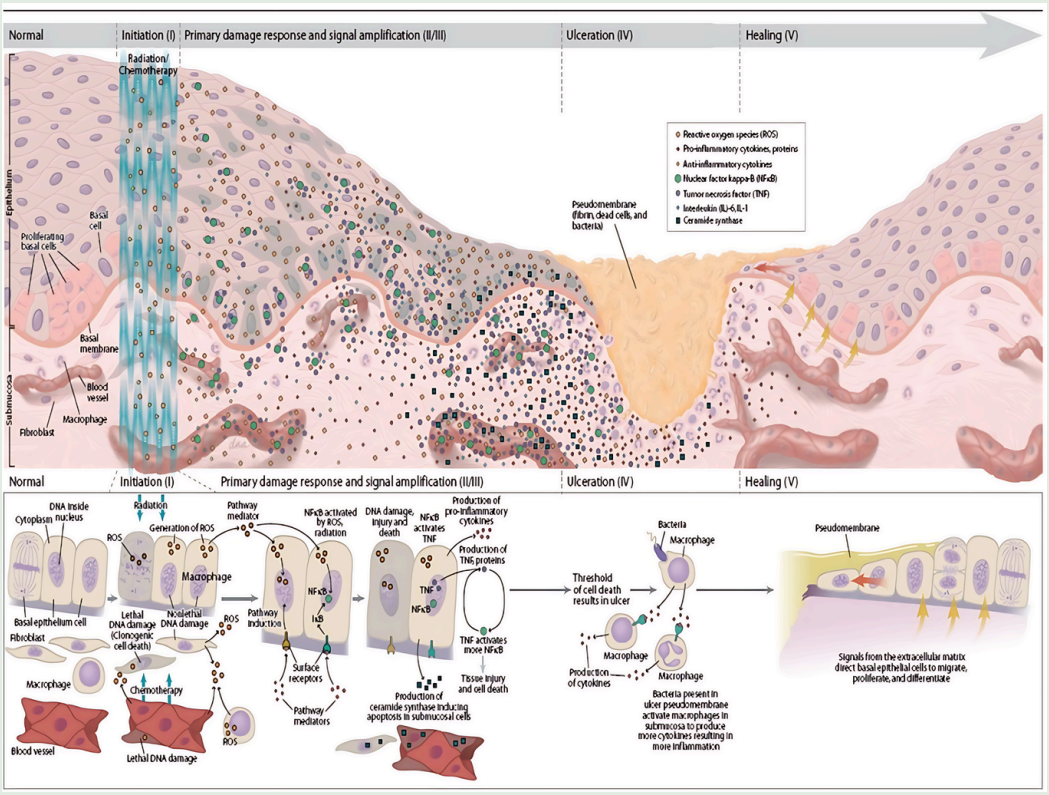


Figure 4. *Mucositis pathogenesis. (Reprinted from Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. J Support Oncol. 2007 Oct;5(9 Suppl 4):3-11.).*

3.5. Assessment of oral mucositis severity

OM assessment scales have been developed as a means of reporting specific treatment-related stomatotoxicity, as nursing management tools, and as efficacy endpoints for anti-mucositis therapies. The most commonly used scales for both toxicity reporting and interventional clinical trials are the WHO, NCI (CTCAE) and RTOG scales. While NCI (CTCAE) criteria are most commonly used to describe the severity of adverse events associated with anti-cancer treatments, it is the WHO scale that have become the gold standard in the assessment of the efficacy of agents targeting oral mucositis. The utility, validity and accuracy of the WHO scale has been demonstrated across numerous clinical trials. The scale has been effective in describing the incidence, severity and trajectory of OM and is sensitive enough to identify and differentiate the effects of interventions on the condition. There is good concordance in identifying severe forms of OM among the WHO, CTCAE, and RTOG scales (Villa et al, 2021). Scales relying on patient-reported outcomes (PROs) have been used to supplement composite or clinician-dependent assessments. PROs in OM trials are indication-specific or a component of comprehensive quality-of-life outcomes. Of the former, the most widely used is the Oral Mucositis Daily Questionnaire (Stiff et al. 2006). Modifications of the instrument have been developed and validated for paediatric use (Tomlinson et al. 2011) and for patients being treated with radiation therapy for cancers of the head and neck (Epstein et al. 2007). Pain related to OM is commonly assessed used in a Visual Analogue Scale (VAS), where patients are asked to rank the severity of their pain on a scale from 0 mm (no pain) to 100 mm (most severe).

4. Disease-modifying treatments for oral mucositis

There are no disease modifying treatments for OM authorised in the EU. Palifermin, a keratinocyte growth factor, is approved in the US to decrease the incidence and duration of severe OM in patients with hematologic malignancies receiving myelotoxic therapy in the setting of autologous hematopoietic stem cell support. The safety and efficacy of palifermin has not been established in patients with non-hematologic malignancies. Palifermin was withdrawn from the EU market in 2016 for commercial reasons (EMA 2016). No other agents in this category are approved for the prevention or treatment of OM. Several agents are in clinical development, so far with mixed clinical and regulatory success. Examples include avasopasem, a superoxide dismutase mimetic whose New Drug Application was refused by the FDA despite positive Phase 3 results because of the requirement for an additional Phase 3 trial. Another example is RRx-001 (bromonitrozidine), a nitrogen-containing hypoxia-activated small molecule with positive Phase 2a results. Other examples include MIT-001 (NecroX7), and EC-18.

Given the mixed results or early stage of these potentially disease-modifying drug candidates, that may take years to reach approval, there will continue to be a need for effective pain management as results show OM is unlikely to be completely avoided.

5. Pain management

Pain, often severe pain, is the dominant manifestation of OM. The use of a stepwise approach to pain management has been suggested, starting with topical anaesthetics such as lidocaine followed by strong, opioid-based analgesics such as fentanyl or morphine, which are needed in up to three-quarters of HNC patients with OM (Brown & Gupta 2020). For many patients, this approach is inadequate or fraught with unacceptable side effects (Zayed et al. 2021). Often, these treatments are applied in a non-specific, prophylactic manner and may require intravenous administration, which is invasive, time-consuming and expensive. There is no treatment such as BupiZenge™, which specifically targets patients with an as-needed dosing commensurate with their subjective pain. There is a large unmet need for an effective, precision medicine, topically applied treatment for OM-related pain.

A detailed description of the current treatment landscape for OM-related pain is provided below in Section 6.2 Available Treatments.

Unmet Medical Need

6. Unmet Medical Need

6.1. Epidemiology

Head and neck cancer is the seventh most common cancer globally, accounting for more than 660,000 new cases and 325,000 deaths annually. The overall incidence of HNC continues to rise, with a predicted 30% increase annually by 2030 (Sung et al. 2021, Johnson et al. 2020). Pain related to OM occurs foremost in HNC patients undergoing chemotherapy and/or radiotherapy. Between 20% to 40% of patients with solid tumours receiving chemotherapy develop mucositis, usually within five to fourteen days of starting treatment (Brown et al. 2020). The incidence and severity of OM vary between chemotherapeutic agents, the number of chemotherapy cycles, the dose of chemotherapy, and from patient to patient (Naidu et al. 2004). Patients who receive myeloablative preparations for hematopoietic stem cell transplant have a higher incidence of OM (Vagliano et al. 2011). One study reported that patients who receive high doses of chemotherapy or undergo bone marrow transplantation have a 76% risk of mucositis. Up to 91% of patients who receive radiation therapy for HNC develop painful OM, which is associated with increased healthcare resource use and excessive healthcare costs (Elting et al. 2007). Radiation-induced oral mucositis (RIOM) occurs in 100% of altered fractionation radiotherapy HNC patients (Maria et al. 2017). The frequency of mucositis is higher in patients with poor nutritional status and inadequate oral care. Younger age patients may have a higher incidence of oral mucositis (Vagliano et al. 2011). Figure 6 illustrates the risk of developing OM associated with different chemo- and radiation therapy regimens used to treat HNC.

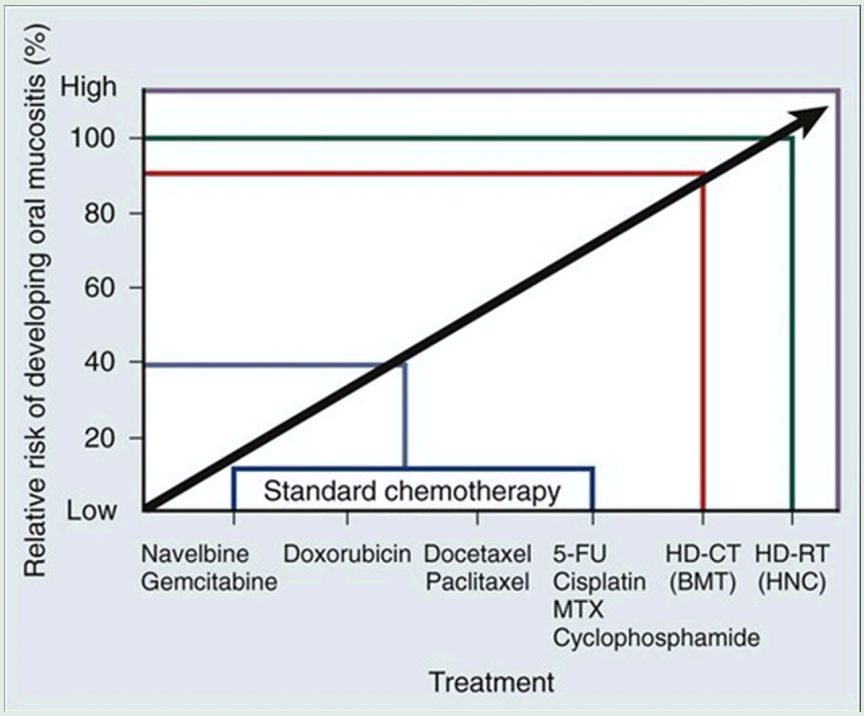


Figure 6. *Relative risk of developing OM associated with different cancer treatment regiments. (Majithia et al. Oral Complications. In: Ed(s): Niederhuber et al. Abeloff's Clinical Oncology (6th Ed.). Elsevier, 2020. Pp:607-620.e6)*

The rise in incidence of HNC cancer is accompanied by a change in aetiology (Sung et al. 2021, Johnson et al. 2020). As smoking rates have declined in Europe and the USA, the importance of smoking as a major cause of HNC has declined. However, increasing incidence rates of HNC in Europe have been attributed to a rise in oropharyngeal cancer, linked to human papillomavirus (HPV) infection (Gillison et al. 2015). There has been a rise in cases among younger women in European countries – possibly explained by gender-specific patterns of tobacco and alcohol consumption as well as HPV infection (Bosetti et al. 2020). HNCs are more common among men than women (with diverging trends) and more common in older age

groups, although oropharyngeal cancer incidence peaks around ten years younger, at around 60-65 years (Gormley et al. 2022). The shift in the dominant aetiology of HNCs in the EU from smoking to HPV infection-related has important consequences beyond the rising incidence due to the ubiquitousness of HPV: HPV-related HNCs present at a significantly younger age (below 65 years, on average), at a time when most individuals are still working full-time. It means that the gender-divide due to the larger proportion of heavily smoking men is declining; a larger proportion of women of younger age are affected. Finally, HPV-related HNCs, regardless of age of onset, have a better survival prognosis (Gormley et al. 2022).

This has important implications for the growing unmet medical need for a treatment for pain related to OM, which most patients treated for HNC will experience: For instance, whilst it might be acceptable to prescribe several weeks of opiate treatment for pain relief to patients who are retired and may have a shorter expected survival, prescribing opiate to younger patients of working age is far more problematic due to the risk of tolerance and dependency. Prolonged (>6 months) use of opiates in previously opioid naïve patients who received radiotherapy is a very real concern that may affect 1 in 8 patients (Smith et al 2019). Opioid addiction can have dramatically negative consequences for individuals' heath and their productivity, with wide ramifications for society and healthcare expenditure. As the demographic profile of HNC patients suffering from OM pain shifts to younger patients of working age, the inadequacy of the current standard of care for OM pain becomes even more poignant as doctors face the dilemma of either prescribing a treatment with potentially long-term negative consequences or to deny suffering patients adequate pain relief.

Targeted pain relief with BupiZenge™ also provides the opportunity to address OM pain as a major reason for breaks in radiation therapy, as each day of disruption is associated with lower chance of survival. Younger patients at time of diagnosis means greater urgency for aggressive cancer therapy, and adequate, local pain relief with BupiZenge™ is likely to support keeping on track the treatment schedule for optimal radiation-mediated tumour kill. Altogether, this strongly underlines the dire need for an effective, opioid-sparing treatment such as the oral lozenge formulation of the known anaesthetic bupivacaine, BupiZenge™, that can be safely administered to all patients and provide reliable pain relief.

6.2. Available treatments

Treatment of pain associated with oral mucositis

Currently available treatment options for pain associated with OM are woefully inadequate. Most patients with OM continue to suffer from severe pain affecting functions such as eating and talking despite the availability of anti-inflammatory agents and local treatments to protect the oral mucosa, as recommended by guidelines (Al-Rudayni et al. 2020). Currently used local analgesic treatments have a short and often insufficient duration of effect and systemic opioids have well known adverse effects and carry the risk of tolerance and dependence development. Systemic opioids are also insufficiently effective for controlling breakthrough pain (Nielsen et al. 2012, Brown & Gupta 2020). For example, a Swedish study assessed in 82 HNC patients undergoing radiotherapy with oral mucositis pain their self-reported outcome one week after receiving individualised care with combinations of acetaminophen, non-steroidal anti-inflammatory agents, and opioids (Ling & Larsson 2011). **Despite a step-wise management approach with treatment escalation if symptoms were not controlled, between 52% and 74% of patients reported either no change or a worsening of their pain in the oral region, depending on the location of the pain (mouth, jaw, or throat). Swallowing of solid foods worsened in a quarter of the patients, and trouble eating anything at all worsened in 26% and remained unchanged in 28% (Ling & Larsson 2011)**. There is a need for more efficacious treatments of the local oral pain caused by OM without disabling systemic adverse effects. BupiZenge™ contains the long-acting analgesic bupivacaine in a lozenge for local oral treatment and has been designed to target this unmet medical need.

Based on a comprehensive systematic review of the literature, the Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) developed clinical practice guidelines for the management of OM (Elad et al. 2020), which recommend pain relief, dietary support, and secondary infection prevention as key elements in management.

Of note, the guidelines published in 2020 have hardly changed from the first edition in 2004; indicating the lack of available evidence of sufficient quality.

The MASCC/ISOO guidelines recommend basic oral care, which includes all measures to reduce the bacterial load in the oral cavity, prevent infection and provide comfort and pain relief. Basic oral care usually comprises mechanical cleaning (e.g. flossing), mouthwashes to reduce bacterial build-up, hydration, and lubrication of the oral mucosal surfaces. Despite being an important best practice for patient care, the MASCC/ISOO study group identified a lack of high-quality rigorous studies, and a review of mixed-medication mouth rinses was excluded due to the heterogeneity of the ingredients. Regarding anti-inflammatory agents, the guidelines recommend benzydamine mouthwash for the prevention of OM. The recommendation for benzydamine is limited to radiation regimens which do not include concomitant chemotherapy. Since the standard of care for HNC is concomitant chemoradiation, the use of benzydamine is very limited. The guidelines also recommend, based on varying levels of evidence, photobiomodulation and cryotherapy in certain circumstances for the prevention and treatment of OM. Regarding pain management in OM, the guidelines suggest 0.2% topical morphine mouthwash. Sucralfate (systemic and topical) – a treatment for duodenal ulcers – is not recommended based on lack of evidence of effectiveness. A previously issued recommendation in favour of using doxepin mouthwash and transdermal fentanyl was removed as the available evidence was equivocal, based on mixed populations or of low quality (Brown & Gupta 2020).

A major challenge for the management of OM – both regarding prevention, treatment, and pain reduction – is the heterogeneity of methods used in clinical practice and clinical studies, as well as the general lack of high-quality evidence from well-controlled trials. This heterogeneity is consistent with a lack of interventions that are predictable and effective. The current standard of care for OM and the treatment of pain related to OM varies between clinicians, patients, geographies and settings. *The recent "opioid epidemic" (CDC 2023) that has developed as a spill-over effect of liberally prescribed opiates for pain relief in recent decades, has added a particular dilemma to the management of OM-related pain: The willingness to prescribe opioid-based pain relief varies strongly between individual physicians, which leaves patients in the worst of situations as either, they risk opioid dependence due to exposure to high-dose opiates for long durations, or they are denied adequate pain relief due to a too restrictive use of opiates. Apart from the variable use of opioid-based pain relief, this fragmented care landscape reflects the fact that most patients do not experience adequate pain relief with acceptable safety risks and side effects with current treatments. Physicians often resort to individualised trial-and-error methods combining, for instance, different anti-inflammatory or analgesic agents in mouthwashes to try and provide patients with adequate pain relief. This non-standardised way of treating OM-related pain, which is not based on high quality evidence, exposes patients to the inherent risks of treatments with unknown efficacy and safety profiles. Thus, a treatment for OM-related pain, such as BupiZenge™, that has minimal side effects and can be taken in a standardized form on an as-needed basis (with a maximum number of daily lozenges) to account for varying levels of pain, and that is supported by high quality, controlled evidence, is much needed.*

A reasonable approach to managing cancer treatment-associated OM pain under current standard of care in Europe and the US as suggested by Brown & Gupta (2020) involves any or all of the following:

For patients with OM caused by chemotherapy:

- Begin with bland rinses and topical anesthetics, such as 2% viscous lidocaine;
- Modify the diet to limit incidental trauma by avoiding rough and sharp foods;
- Avoid alcohol;
- Treat pain with limited risk for systemic absorption using 2% morphine mouthwash;
- Consider admission to the hospital for systemic analgesics and ongoing monitoring and evaluation for secondary infections in patients with severe mucositis or who are unable to tolerate any oral intake;
- Use patient-controlled analgesia with morphine which has good evidence to support its use in hospitalized patients;
- Use transdermal formulations of morphine or fentanyl to provide long-lasting background pain control and patient-controlled analgesia for management of breakthrough pain.

The fact that OM is in many patients expected to become so severe as to require hospitalization for pain relief with systemic analgesic and opioid-based treatments is a stark illustration of the inadequateness of the current standard of care and the huge unmet medical need.

So-called magic mouthwashes (which typically contain mixtures of topical anaesthetics, antihistamines, and/or steroids) are frequently used, but these mouthwashes are neither standardized with regards to component ingredients or ratios, nor more effective than bland rinses in reducing mucositis pain, and they carry the additional risk of systemic toxicity (Besinger et al 2008; Uberoi et al. 2019). Viscous lidocaine solutions, swish and spit, are effective at providing topical anaesthesia but can numb the entire mouth, provide too short durations of adequate pain relief, and place patients at risk for accidental trauma (Besinger et al 2008; Brown & Gupta 2020).

For patients with OM caused by radiation, a similar approach is reasonable (Brown & Gupta 2020):

- Bland rinses, such as normal saline and salt-and-soda mouthwashes, swish and spit;
- Topical anesthetics, such as 2% viscous lidocaine swish and spit;
- Low-level laser therapy as frequently as every day;
- Systemic agents, including opiates (2% morphine mouthwashes.

Patients who develop radiation-induced OM will likely require long-acting opiates with the option for a short-acting agent for breakthrough pain until the mucositis resolves (Mallick et al. 2016).

Mouthwashes that contain the tricyclic antidepressant doxepin have also been trialed in radiation-induced mucositis. The Alliance trial (NCCTG-N09C6) provided initial support for the use of a doxepin rinse for reducing mouth pain from radiation-induced mucositis in patients with HNC compared with placebo (Leenstra et al. 2014). A follow-up study by the same investigators, Alliance A221304, compared a doxepin mouthwash or diphenhydramine-lidocaine-antacid combination mouthwash to placebo for reducing pain in patients with HNC who underwent radiotherapy. Both treatment groups experienced identical pain relief, which was statistically significantly better than the placebo group. However, the trial failed to meet its prespecified threshold for clinical significance. Of note, patients who received the doxepin mouthwash experienced more drowsiness, unpleasant taste, and stinging or burning than those in the combination mouthwash or the placebo groups (Sio et al. 2019). As such, doxepin rinses lack sufficient evidence of efficacy and safety, and before initiating doxepin mouthwashes, patients should be counseled on toxicity, and adverse effects should be monitored. (Sio et al. 2019; Leenstra et al. 2014). Topical antibiotics, sucralfate, and misoprostol are not recommended for the treatment of radiation-induced mucositis. Cholinergic agents such as pilocarpine are also not recommended to treat radiation-induced mucositis (Brown & Gupta 2020).

In the initial stages of OM associated with radiotherapy (usually below a cumulative dose <20 Gy), mucosal burning may respond to over-the-counter analgesics such as acetaminophen or ibuprofen or topical anaesthetics or coating agents such as GelClair or MuGard (Elad et al. 2020). Breaches in mucosal integrity (typically at cumulative doses of 20–30 Gy) are accompanied by escalating pain for which oral narcotics may be helpful initially and then more aggressive systemic opioids (fentanyl or morphine) may be required. Morphine mouthwashes have shown some efficacy in mitigating OM related pain in HNC patients receiving radio-chemotherapy (Cerchietti et al. 2002), as well as in cases of OM associated with HSCT conditioning regimens (Nielsen et al. 2012). Yet, despite maximum tolerated opiate treatment, breakthrough pain is common. **A major concern with any opiate treatment is tolerance and the risk for dependency. This is particularly poignant as HNC patients may include young, active persons who are productive members of the work force and have a long life expectancy.**

Disease-modifying treatments for oral mucositis

A number of topical formulations have been assessed as mucositis interventions. Benzydamine hydrochloride is a locally acting nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgetic properties (Turnbull et al. 1995). Oral rinses containing benzydamine hydrochloride are indicated for the relief of painful inflammatory conditions of the mouth and throat and are marketed in several European countries. Examples of treatment authorised in the EU include Difflam Oral Rinse or Tantum Verde. Use of an oral rinse containing benzydamine hydrochloride decreased the incidence of OM in a randomized, placebo-controlled trial of HNC patients receiving radiotherapy but was ineffective when concomitant chemotherapy was included in the regimen (Epstein et al. 2001). The results of a Phase 2 trial suggested that a novel, mucoadhesive topical troche (Validive) containing clonidine might be effective in reducing the incidence and course of OM in patients receiving chemoradiation for HNC (Giralt et al. 2020). However, in a planned Phase 2/3 clinical trial of Validive, the trial's sponsor, Monopar, stopped the study when prespecified efficacy endpoints were not met and announced its plan to discontinue development.

To date, the only biologics agent approved for the treatment of OM is Kepivance (palifermin; Amgen), recombinant keratinocyte growth factor-1. Clinical trials for both chemotherapy and radiation therapy induced OM demonstrated efficacy (Spielberger et al. 2004; Le et al. 2011). After receiving marketing authorisation in the EU in 2005, Kepivance was withdrawn from the EU market 2016 at the request of the marketing authorization holder. Palifermin is not indicated for the treatment of OM caused by cancer treatments for solid tumours because of concerns that it protects them (as well as healthy tissues) from the effects of chemotherapy and radiation (Oronsky et al. 2018). Currently, several mechanistically based systemic therapies are in different stages of clinical development. These include avasopasem manganese (by Galera Therapeutics; whose NDA was rejected by the FDA despite positive results in a Phase 3 trial because of the requirement for a second Phase 3 trial), EC-18 and nibrozetone (by EpicentRx; both with positive Phase 2 results), ST-617 (by Supportive Therapeutics).

6.3. Patient reported pain with today's Standard of Care

Characterizing pain during Radiation Therapy (RT) for oral cavity/oropharyngeal cancer (OC/OPC) is a clinical challenge due to its multifactorial etiology and variable management. A study has been performed with the aim to define pain profiles through temporal characterization of pain descriptors, physiologic state, and RT-induced toxicities for pain trajectories. The study "Temporal characterization of acute pain and toxicity kinetics during radiation therapy for head and neck cancer. A retrospective study" was published in Oral Oncology Reports 7 (2023) covering 351 OC/OPC patients treated with RT between 2013 to 2021. Weekly numeric scale pain scores, pain descriptors, vital signs, physician-reported toxicities, and analgesics were analyzed.

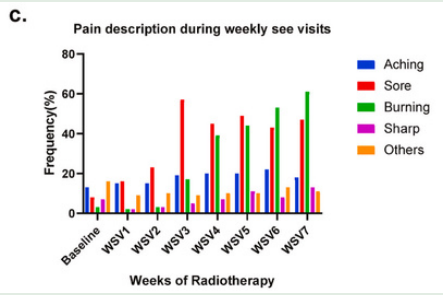
Table 2
Patient reported pain trajectory and pain profiles during the weekly see visits (WSVs).

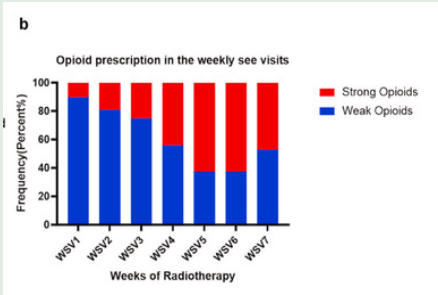
Table:	Baseline	WSV1	WSV2	WSV3	WSV4	WSV5	WSV6	WSV7
Patients reported pain score (n, %)	341 (97%)	351 (100%)	351 (100%)	351 (100%)	330 (94%)	318 (91%)	303 (87%)	159 (45%)
Mean pain score (SD)	1.4 (2.3)	1.1 (1.8)	1.6 (2.0)	3 (2.5)	4 (2.5)	4.2 (2.6)	4.7 (2.7)	5.5 (2.8)
Median pain score	0	0	1	2	4	4	5	5
Pain location (n, %)								
Mouth	33 (10%)	50 (14%)	90 (26%)	181 (52%)	208 (63%)	202 (64%)	200 (66%)	96 (60%)
Throat	27 (8%)	68 (19%)	106 (30%)	167 (48%)	210 (64%)	195 (61%)	255 (84%)	119 (74%)
Skin	0 (0%)	5 (1%)	9 (3%)	38 (11%)	55 (17%)	90 (28%)	105 (34%)	67 (42%)
Other	69 (20%)	39 (11%)	43 (12%)	35 (11%)	34 (10%)	26 (8%)	33 (11%)	16 (10%)
Pain description (n, %)								
Aching	45 (13%)	53 (15%)	53 (15%)	68 (19%)	65 (20%)	64 (20%)	68 (22%)	29 (18%)
Sore	28 (8%)	56 (16%)	81 (23%)	143 (57%)	146 (45%)	156 (49%)	132 (43%)	76 (47%)
Burning	11 (3%)	7 (2%)	11 (3%)	60 (17%)	130 (39%)	140 (44%)	161 (53%)	97 (61%)
Sharp	25 (7%)	6 (2%)	11 (3%)	17 (5%)	24 (7%)	36 (11%)	25 (8%)	21 (13%)
Other	55 (16%)	28 (9%)	35 (10%)	32 (9%)	34 (10%)	31 (10%)	40 (13%)	18 (11%)
Pain onset (n, %)								
Ongoing	45 (13%)	78 (22%)	105 (30%)	158 (45%)	186 (56%)	198 (62%)	203 (67%)	112 (70%)
Gradual	9 (3%)	14 (4%)	13 (4%)	17 (5%)	19 (6%)	10 (3%)	5 (2%)	0 (0%)
Progressive	0 (0%)	0 (0%)	3 (1%)	5 (2%)	9 (3%)	11 (4%)	11 (4%)	9 (6%)
Sudden	4 (1%)	2 (0.5%)	4 (1%)	3 (0.9%)	1 (0.3%)	0 (0%)	2 (0.6%)	0 (0%)
Other	5 (2%)	1 (0.3%)	2 (0.6%)	3 (0.9%)	1 (0.3%)	0 (0%)	1 (0.3%)	1 (0.6%)
Frequency (n, %)								
Intermittent	36 (10%)	69 (20%)	95 (27%)	118 (34%)	136 (41%)	117 (37%)	103 (34%)	52 (33%)
Constant/continuous	56 (16%)	25 (7%)	39 (11%)	74 (21%)	93 (28%)	105 (33%)	126 (42%)	72 (45%)
Progression (n, %)								
Gradually improving	0 (0%)	13 (4%)	10 (3%)	4 (1%)	9 (3%)	8 (3%)	8 (3%)	4 (3%)
Rapidly improving	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)
Gradually worsening	28 (11%)	15 (4%)	38 (11%)	107 (30%)	118 (36%)	132 (42%)	131 (43%)	64 (40%)
Rapidly worsening	0 (0%)	0 (0%)	1 (0.3%)	2 (0.6%)	5 (1.5%)	0 (0%)	4 (1.3%)	1 (0.6%)
Not changed	39 (11%)	57 (16%)	69 (20%)	58 (17%)	64 (19%)	62 (19%)	54 (18%)	44 (27%)

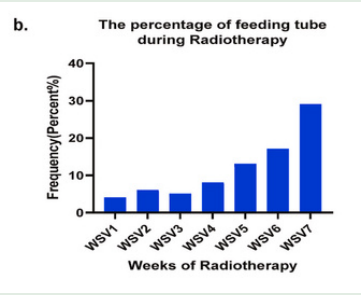
Abbreviations: n = number, % = percentage. Note: the number and the percentages are based on the total number of patients reported pain each week.

Figure 7. *Patient reported pain trajectory and pain profiles during Weekly See Visits (WSVs). (Temporal characterization of acute pain and toxicity kinetics during radiation therapy for head and neck cancer. A retrospective study. V. Salama, S. Youssef, T. Xu et al, Oral Oncology Reports 7 (2023))*

The report concludes: **"Results demonstrate a significant temporal increase in the severity of pain and other radiation treatment-related acute toxicities throughout the course of RT/CRT in OC/OPC patients and an ongoing need for better and safer pain control in this population".**







These unsatisfactory patient reported results considers the full use of topical anesthetics, weak opioids and strong opioids available under today's Standard of Care.

To summarise, the current treatment landscape for OM is characterised by lack of standardized, effective, well-tolerated and safe options. In particular the pain associated with OM continues to represent a significant unmet medical need as it affects patients on multiple levels, including impaired psychological and physical quality of life, and adverse effects on their cancer treatment and hence, potentially, survival.

6.4. Healthcare costs associated with pain related to oral mucositis

Oral mucositis adds significantly to the incremental costs of cancer care as a consequence of increased medication use, placement and maintenance of parental feeding dependence, increased physician office visits and emergency room use, and hospitalizations for pain management, hydration, and nutrition. In a systematic review of peer-reviewed studies published until 2017, Elting & Chang (2019) estimated the incremental cost of OM as a complication of cancer therapy being USD $5,000–$30,000 among patients receiving radiation therapy and USD $3,700 per cycle among patients receiving chemotherapy. The incremental cost of OM-related hospitalization among stem cell transplant recipients was estimated to exceed USD $70,000. Another recent systematic review by Rodrigues-Oliviera et al. (2021) found that the costs attributable to mucositis in the hematopoietic stem cell transplantation setting ranged from several thousand to up to over USD $200,000 er patient. Radiotherapy, chemoradiotherapy, and radiotherapy plus molecular targeted therapy accounted for OM costs up to USD $33,000 per patient. Costs for mucositis in the chemotherapy setting amounted to up to USD $32,000 per patient (Oliveria et al. 2021).
As described in Section 2.1.1., up to 40% of patients receiving chemotherapy for solid tumours, and virtually all patients receiving radiation therapy for HNC develop OM of clinical significance. With 890,000 new cases of HNC worldwide annually, the enormous economic scale of avoidable healthcare expenditure associated with OM-related pain that is not controlled by currently available treatment option becomes obvious (Barsouk et al. 2023)

6.5. Summary of the unmet medical need

As outlined above, current treatment options for OM-related pain are woefully inadequate and leave a large unmet medical need that the Applicant's product, BupiZenge™, is being developed to address. The unmet need and major public health interest is evident and summarised in the following points.

- *Current treatment approaches lack standardisation, vary widely between patients and physicians, are based on low-quality or insufficient evidence of safety and effectiveness, and may expose patients to difficult-to-estimate safety risks.*
- *Current treatment and investigational options are based on a "one size, fits all" approach. Individualising treatment to target individuals most at risk with the optimum dose and timing of interventions is lacking.*
- *Current treatment approaches do not provide adequate pain relief for a sufficient duration of time and with an acceptable side effects profile for most patients with OM.*
- *The average demographics of patients with OM-related pain is shifting towards younger age groups, especially in the HNC population. Also, the age of retirement in Europe has been increasing in most countries. This means that pain relief treatments, such as systemic opiates, that have significant long-term risks of dependency and tolerance, become less and less acceptable. Such treatments can have wider implications on a society's productivity and healthcare expenditure related to the consequences of opioid dependence.*
- *The "opioid epidemic", particularly in the United States, clearly shows the dangers of a liberal use of opioids. Yet, for many OM-pain patients, opiates might be the only currently available treatment providing adequate pain relief. There has been a strong push from the healthcare community and governments to reduce the prescription of opiates. In the current standard of care, patients and physicians find themselves between a rock and a hard place: adequate pain relief at the risk of long-term health risks from opioid abuse and dependency, or inadequate pain relief from withholding of opioid-based treatments.*
- *OM-related pain is the pivotal symptom which drives bad health and economic outcomes and has significant negative consequences for patients' physical and social well-being. Severe OM can lead to an inability to eat, leading to involuntary loss of weight and a need to gastrostomy nutrition in some patients. This in turn has negative consequences for cancer patients' overall survival as frailty is associated with worse outcomes. OM-related pain can become so severe as to require patients to interrupt their ongoing cancer treatment, which can have significant negative consequences for the outcome of cancer treatment and unnecessarily prolong chemo/radiotherapy.*

- *Another consequence of the weakened physical state of patients unable to consume sufficient nutrient because of OM-related pain is a potential weakening of their immune system (Wu et al. 2023). This can support a vicious, self perpetuating cycle in OM where inflammation and tissue damage lead to ulceration and subsequent bacterial colonization leading to reinforced inflammatory cytokine mediated damage. An effective treatment for OM-related pain and the resulting stronger physical state of the patient can therefore potentially weaken the vicious cycle in OM and shorten the overall duration of OM (with a net disease-modifying effect; Georgiou et al. 2012).*

- *OM-related pain has significant negative psychological consequences. It can disrupt activities of daily living, sleep, and make it difficult to speak. This adds insult to injury for these patients who are already having to cope with the reality of a cancer diagnosis and all the other side effects of their treatment.*

7. Conclusion and claim of major public health interest

Pain due to oral mucositis is a serious and debilitating condition affecting most patients undergoing chemotherapy and/or radiotherapy for head and neck cancer. It can have severe negative consequences for affected individuals on multiple levels. Pain due to OM significantly impairs patients' psychological and physical well-being; making it difficult to eat, speak and sleep. Pain due to OM can be so severe as to prevent patients from eating properly and can lead to unintentional weight loss and the need for nutritional support via a feeding tube. Adequate nutrition is particularly important for cancer patients, as cancer therapy itself can cause weight loss, and physical stamina is an important positive predictor for better treatment outcomes. Inadequate nutrition can also weaken the immune system and perpetuate a vicious cycle of inflammation and infection that may prolong OM. Treating OM-related pain could therefore potentially lead to better cancer outcomes and shorten OM duration. Finally, pain due to OM can be so unbearable as to require cancer treatment interruptions with potentially detrimental effects for cancer progression and survival. All of these consequences can severely impair patients' ability to function and receive effective treatment for their cancers, which has consequences for healthcare resource utilization and productivity loss, making badly controlled pain due to OM a major public health problem that urgently needs to be addressed. It is estimated that billions of Euros are spent on the management of OM every year in the EU; and an effective treatment is predicted to lead to significant reductions in OM-related societal costs.

Currently available treatment options are woefully inadequate. There are no disease-modifying treatments for OM currently authorized in the EU. Locally applied mouth washes usually do not provide adequate pain relief for durations that are far too short to suppress the constant and breakthrough pain caused by OM. More potent pain relief medications that are often administered systemically may provide temporary pain relief but are associated with safety risks and often unacceptable side effects. Opiates in particular carry a risk of tolerance induction where larger and larger doses are needed to achieve the same pain relief, as well as a risk of dependency when taken over prolonged periods of time (as is the case in patients with pain related to OM). Over recent years, the average age of patients with OM-related pain has been declining, making the cautious use of opioid-based pain relief even more important, as dependency, side effects and overdose can have detrimental consequences for both affected individuals and their continued productive lives in society. An effective and safe, non-opioid-based treatment option is direly needed.

In summary, there is a large unmet clinical need of major public health proportions for a safe, effective, and well-tolerated, locally acting treatment that can suppress the pain related to OM and be administered on an as-needed basis to reflect the high inter-individual variability in pain manifestations. BupiZenge™ is being developed as an innovative oral lozenge formulation of the well-known local anaesthetic bupivacaine with decades of real-world experience in other indications to address this unmet medical need.

BupiZenge could offer substantial benefits compared to today's "one-size fits all" standard of care in two ways: first, consistent with the concept of precision medicine, it is used specifically in those patients whose symptom progression warrants intervention, and the as-needed dosing can be tailored to individuals; second, it should prevent the onset of use and/or the intensity and duration of use of systemic opioid analgesia.

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9. Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CDER	Center for Drug Evaluation and Research
CNS	Central Nervous System
CRT	Concomitant chemoradiation therapy
CT	Chemotherapy
CTAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
FAS Full	Full Analysis Set
FDA	U.S. Food and Drug Administration
Gy Gray	Gray (unit of radiation)
HNC	Head and Neck Cancer
IMP	Investigational Medicinal Product
IMRT	Intensity-modulated Radiation Therapy
IND	Investigational New Drug
KGF	Keratinocyte Growth Factor
LLOQ	Lower Limit of Quantification
MMRM	Mixed Model for Repeated Measures
MPA	Medical Products Agency
NCI	National Cancer Institute
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-Inflammatory Drug
OC	Oral cavity
OM	Oral Mucositis
OMAS	Oral Mucositis Assessment Scale
OMDQ	Oral Mucositis Daily Questionnaire
OPC	Oropharynx
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient Reported Outcome
RT	Radiotherapy
RT-CT	Radiotherapy and Chemotherapy
RTOG	Radiation Therapy Oncology Group
SOC	Standard of Care
SOM	Severe Oral Mucositis
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
QoL	Quality of Life
WHO	World Health Organization

BupiZenge™ - Potential to be the leading treatment for oral pain.

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OncoZenge develops a novel, effective, safe and well-tolerated treatment for oral pain in conditions where currently available treatment options either do not achieve sufficient pain relief or are associated with significant side effects. BupiZenge™ is a new oral lozenge formulation of bupivacaine, an anaesthetic with decades of clinical experience. OncoZenge's lead indication is oral pain due to an inflammatory condition called oral mucositis that affects millions of patients receiving cancer treatment. Oral mucositis causes profound physical and psychological suffering, and is a large unmet medical need for an effective, opioid-sparing treatment option. BupiZenge™ has shown significantly better pain relief compared to standard of care in this indication in a Phase 2 trial.

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