Confirmatory phase 3 trial of lozenge-formulated bupivacaine (BupiZenge) for treatment of oral mucositis pain: design and rationale

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BupiZenge as a potential treatment for oral mucositis pain

The lozenge tablet BupiZenge slowly dissolves over several minutes in the mouth. It releases the non-opioid, long-acting local anaesthetic bupivacaine. Bupivacaine is a local anesthetic with a well-established real-world safety profile in approved intrathecal and epidural products. Bupivacaine is not currently available in lozenge formulation use in the oral cavity, making BupiZenge a novel approach for providing localized and sustained oral pain relief.

BupiZenge has been specifically developed to achieve safe, well-tolerated and lasting local pain relief in the oral cavity. Previous clinical results in Phase 1 and 2 in patients with head and neck cancer (HNC) and oral mucositis (OM) pain support its potential efficacy and safety for achieving more effective and longer lasting pain relief than current standard of care, and to potentially reduce the need for opioid treatment.

Oral mucositis pain

Most patients with HNC receiving radiation therapy develop OM as a painful side effect of the treatment. Oral mucositis is characterized by erythema (redness) and ulceration (mouth sores) of the oral mucosa. The WHO scale distinguishes 4 progressive stages (see box to the right).

As pain intensifies, patients often struggle to eat, resulting in dehydration, weight loss, and impaired quality of life. Progression to Grade 3 or 4 OM can lead to a need for enteral or parenteral nutrition. OM-related pain may require high doses of opioids and may lead to interruptions of cancer therapy, which can negatively affect treatment outcomes and survival. While standard management includes oral rinses and topical/systemic analgesics, most patients ultimately require opioids as OM severity increases.

Current treatment practices vary widely across countries and institutions, underscoring the unmet need for a standardized, effective, non-opioid, and non-steroidal treatment option.

Impact of oral mucositis pain

No escape

For some cancers like head and neck cancer, up to 90% of all patients receiving standard treatment suffer from OM, with no good treatment options.

Quality of life

Studies have shown significant impact on patients' mental, physical and social well being due to the oral pain.

Affecting outcomes

Severe oral pain impacts patients' ability to eat, drink, sleep and socialize. Interrupted or reduced treatments and weight loss may impact cancer patients' prognosis and have significant personal and health-economic consequences.

Pivotal Phase 3 study

The sponsor, OncoZenge AB (publ.), based in Stockholm, Sweden, is preparing a registrational, randomized, open-label, active comparator arm study to confirm the efficacy and safety of BupiZenge lozenge for the treatment of OM pain in patients with head and neck cancer. The study is planned as a global, multi-centre trial, and is based on learning from the Phase 2 trial suggesting efficacy of BupiZenge in the indication. BupiZenge lozenges will be compared to lidocaine gel, both taken as needed up to 8 times per day. The target sample size is 150 patients and the trial is designed for European marketing authorisation. The Sponsor OncoZenge is actively evaluating collaborations towards an approval in the United States.

The trial will enrol women and men of adult age, diagnosed with HNC and scheduled for definitive or post-operative radiotherapy with or without concurrent chemotherapy. The treatment length is 6 weeks and patients are only enrolled into the treatment phase once they develop OM of Grade 1 or higher and score their oral pain as at least 4 on a 11-point numerical rating scale.

Study Objectives

Primary objective is to evaluate the effect of BupiZenge compared to lidocaine in treating oral cavity pain.

Primary endpoint: is the average on-treatment patient-reported oral cavity pain intensity and duration assessed one hour after a dose during the first 2 weeks after randomization. During the first 14 days after treatment initiation, starting on Day 2, participants will rate their pain on an NRS 60 minutes after a dose, 3 times a day, every second day. If fewer than 3 doses are taken on a given day, pain assessments will only be performed at the times of actual dosing, and unused time points will be excluded. Memory aid strategies (e.g. push notifications) will be used to support compliance.

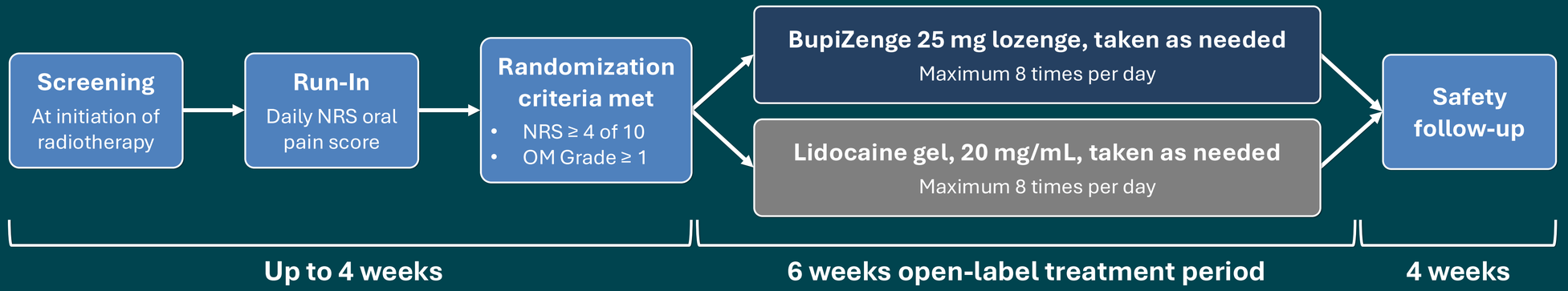
Important secondary objectives and endpoints include safety and tolerability, consumtion of systemic opioids, patient-reported quality of life, patients' ability to eat and drink, the progression of oral mucositis, and pharmacokinetics (assessed in a subset of patients).

Key inclusion criteria

- Individuals aged 18-80 years with histologically diagnosed with squamous cell HNC undergoing or about to start intensity modulated radiotherapy (IMRT) with a life expectancy of at least 6 months.
- Must not have pre-existing oral or pharyngeal pain, previous radiation therapy to the head or neck area, be receiving high-dose corticosteroids, oral or pharyngeal pain exclusively attributable to the primary tumor or surgical wound rather than OM, or be taking opioids for any reason prior to study start.

Randomization criteria

- New onset oral and/or pharyngeal pain due to OM rated as 4 or higher on an 11-point NRS at least once since starting HNC treatment
- Oral mucositis Grade of 1 or higher



Disclosures

Christoph Nowak is remunerated by, and owns shares in, the sponsor of the study, OncoZenge. Stephen T. Sonis has received consulting fees from OncoZenge via Primary Endpoint Solutions LLC.

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