NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2020

Dusquetide for chemoradiation-induced oral mucositis in patients with squamous cell carcinoma of the head and neck

NIHRIO ID	10868	**NICE ID**	9971
Developer/Company	Soligenix Inc	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Dusquetide is in clinical development for the treatment of chemoradiation induced oral mucositis (OM) in patients with squamous cell carcinoma of the head and neck. OM is the most common toxicity in patients with head and neck cancer who are treated with chemoradiation, which not only impairs their function and quality of life but also affects their survival and outcomes from the disease. OM is characterised as an inflammation of the oral and gastrointestinal mucous membranes accompanied by many complex mucosal and submucosal changes. Symptoms of OM vary from pain and discomfort to an inability to tolerate food and fluids.

Dusquetide is administered intravenously. It works by controlling the immune response system and intracellular signalling pathways. Dusquetide is effective in reducing inflammation, reducing bacterial infection and aiding in the tissue healing. If licensed, dusquetide may offer a treatment option for OM in patients with concomitant chemoradiation treatment for squamous cell carcinoma of the head and neck.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of oral mucositis (OM) in patients with concomitant chemoradiation therapy for squamous cell carcinoma of the head and neck.[1]

TECHNOLOGY

DESCRIPTION

Dusquetide (SGX942) is a first-in-class Innate Defense Regulator (IDR) that modulates the innate immune response to both pathogen-associated molecular pattern (PAMPs) and damage-associated molecular patterns (DAMPs) by binding to p62, a key adaptor protein that functions downstream to the key sensing receptors that trigger innate immune activation. Dusquetide controls the cellular signalling from pro-inflammatory, pro-macrophage response to an anti-inflammatory, heightened pro-macrophage response, which leads to decreased inflammation with increased bacterial clearance and tissue healing.[2]

Dusquetide is in clinical development for the treatment of OM in patients with concomitant chemoradiation therapy for head and neck cancer.[1] In phase III clinical trial (DOM-INNATE; NCT03237325), patients received an intravenous infusion of dusquetide at a dose of 1.5 mg/ml twice a week starting within 3 days after initiating radiation therapy and continuing through 2 weeks after radiation therapy ends.[1]

INNOVATION AND/OR ADVANTAGES

Dusquetide belongs to a new class of short, synthetic peptides. It has a novel mechanism of action whereby it modulates the body's reaction to both injury and infection towards an anti-inflammatory, anti-infective and tissue healing response by binding to a protein known as p62. There are no other drugs that target the p62 protein.[2,3] Dusquestide modulates the response of the innate immune system in response to various stimuli, including infection, tissue damage and inflammation. It also accelerates the resolution of tissue damage following exposure to a variety of agents including bacterial pathogens, trauma and chemo and/or radiation therapy.[3]

Dusquetide, has the potential to address each of the stages of the pathogenesis of oral mucositis by decreasing the innate immune amplification of damage signalling (and subsequent exacerbation of tissue damage), decreasing the incidence and increasing the clearance of any secondary infections aiding in the tissue healing and resolution of mucositis.[2]

Dusquetide has demonstrated efficacy in preclinical models emphasising all three aspects of its activity.[3] Furthermore, in a phase II clinical study evaluating a dose of 1.5 mg/kg, dusquetide successfully reduced the median duration of severe oral mucositis by 67% in patients receiving the most aggressive chemoradiation therapy for the treatment of their head and neck cancer. In addition to OM findings, increased incidence of complete response of tumour, decrease in infection rate and an increased 12-month survival were observed with dusquetide treatment.[3,4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Dusquetide does not currently have Marketing Authorisation in the EU/UK for any indication.

Dusquetide has received promising innovative medicine (PIM) designation in the UK in December 2016.[5]

Dusquetide has received Fast Track designation by US FDA in June 2013 for the treatment of oral mucositis as a result of radiation/or chemotherapy in head and neck cancer.[6]

The safety of single and multiple ascending doses of intravenous (IV) dusquetide was demonstrated in a placebo-controlled study of 84 healthy human volunteers, in which dusquetide was found to be safe and well tolerated. In the groups receiving multiple doses, most adverse events (AEs) were related to minor infusion/venipuncture reactions. Other reported AEs were somnolence (4/20 dusquetide patients, 2/10 placebo patients), alanine aminotransferase (ALT) elevation (3/20 dusquetide patients, 1/10 placebo patients), and back pain (3/20 dusquetide patients, 1/10 placebo patients).[2]

PATIENT GROUP

DISEASE BACKGROUND

Oral mucositis (OM) is one of the most common side effects of chemo and radiotherapies of the various head and neck cancers.[7] OM is characterised by inflammatory and ulcerative reactions in the oral cavity.[8] The epithelial cells of the oral mucosa undergo rapid turnover, usually every 7 to 14 days, which makes these cells susceptible to the effects of cytotoxic therapies. Both chemotherapy and radiation therapy can interfere with the maturity and cellular growth of epithelial cells, causing changes to normal turnover and cell death.[9] OM incidence for all grades in head and neck cancer patients is approximately from 59%-100% after receive radiotherapy or chemoradiation.[10]

Some of the major risk factors include age, nutritional status, type of malignancy, oral care during treatment, and neutrophil count before treatment. In general, younger patients are more prone to mucositis because of rapid epithelial mitotic rate, or the presence of more epidermal growth factor receptor.[9]

OM can occur shortly after chemotherapy administration, with a peak in symptoms between 7 and 14 days after treatment. Symptoms typically resolve 14 to 21 days after treatment. The onset of symptoms for radiation-induced OM occurs 2 to 3 weeks after the first treatment and continue during radiation therapy. OM has a profound effect on the quality of life it is typically very painful and can be highly painful. Severe OM can result in swallowing impairment and/or pain that prevents oral intake results in weight loss, anorexia, malnutrition, anaemia, and fatigue and frequently requires chemotherapy or radiation treatment modification, interruption, or discontinuation.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In general, OM occurs in more than 90% of patients who receive radiation or chemotherapy for head and neck tumour. It occurs in almost all the patients who are treated for cancers of mouth, oropharynx, nasopharynx and in approximately two-thirds of those for cancers of the hypopharynx or larynx.[12]

Data from patients in England treated with chemotherapy between 2013 and 2015 for malignant tumours of the oral cavity, oropharynx and other head and neck suggest that 6,864 and 11,557 received chemotherapy and radiotherapy respectively as part of their treatment.[13] Applying the prevalence estimated from above, between 6,177 and 10401 head and neck patients in England that received chemotherapy and radiotherapy respectively as part of their treatment would develop OM.

Studies suggest that chemoradiation induced OM presents a significant burden for cancer patients and can increase hospital stay.[8,14,15]Another study has reported, OM incidence for all grades from range 59.4% to 100% when follow-up after radiotherapy or chemoradiotherapy.[10]

Hospital episode statistics (HES) for England 2018-19 recorded 1,409 finished consultant episodes, 1,169 admissions for oral mucositis (ulcerative) as primary diagnosis (ICD-10 code K12.3), resulting in 4,997 bed days and 280 day cases. The HES for the same time period recorded an overall total of 11,009 cases of OM as all diagnosis.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Although its complex biological nature makes the conventional management of OM a challenge, many strategies are used to minimise the adverse effects of anticancer treatment, includes patient education, non-medicated saline rinses, dose reduction and other both therapeutic and preventive measures.[12,17]

The common treatment and preventive measures include comprehensive oral hygiene, good hydration, a bland soft diet and avoiding alcohol and tobacco may increase the person's comfort. Ice, water-based moisturisers, painkillers and non-steroidal anti-inflammatory drugs can help reduce symptoms. Antibiotics may be needed to treat infectious complications. Drugs can be sometimes used to prevent or treat OM.[18]

Given the number of variables involved in the development of mucositis, it is unlikely that any one prophylactic or treatment regimen will prove suitable for all patients.[19] Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy is currently recommended as an interventional procedure.[8]

CURRENT TREATMENT OPTIONS

Currently, there are no NICE recommended medicines for the treatment of chemoradiation induced OM for squamous cell carcinoma of the head and neck.

PLACE OF TECHNOLOGY

If licensed, dusquetide will offer a treatment option for chemoradiation induced OM for squamous cell carcinoma of the head and neck patients.[1]

CLINICAL TRIAL INFORMATION

Trial	DOM-INNATE,NCT03237325; A pivotal, double-blind, randomized, placebo-controlled, multinational study of SGX942 (dusquetide) for the treatment of oral mucositis in patients being treated with concomitant chemoradiation for the treatment of squamous cell carcinoma of the head and neck **Phase III**- Ongoing **Location(s):** EU (including UK) and USA

Trial design	Randomised, parallel assignment, quadruple blinding
Population	N= 260 (planned); squamous cell carcinoma of the oral cavity or oropharynx without distant organ metastases
Intervention(s)	Dusquetide • Patients received intravenous infusion of dusquetide at a dose of 1.5 mg/ml twice a week starting within 3 days after initiating radiation therapy and continuing through 2 weeks after radiation therapy ends
Comparator(s)	Placebo • Placebo is 0.9% sodium chloride (normal saline). The treatment preparation, frequency and duration of therapy are identical to that of the active drug.
Outcome(s)	Duration of severe oral mucositis (SOM) [Time frame: approx. 13 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of dusquetide is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Interventional procedures guidance. Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy (IPG615). May 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- Not relevant guideline was identified

OTHER GUIDANCE

- UK Oral Management in Cancer Care Group. Oral Care guidance and support in cancer and palliative care. Third Edition. June 2019.[20]
- NHS Royal Cornwall Hospitals. NHS Trust. Prevention and Treatment of Oral Complications and Oral Mucositis for Patients Receiving Systemic Anti-Cancer Treatment (SACT) Clinical Guideline. June 2019.[21]
- Royal College of Surgeons. The Oral Management of Oncology Patients Requiring Radiotherapy, Chemotherapy and / or Bone Marrow Transplantation. Updated 2018.[21]
- European Society of Medical Oncology (ESMO) clinical practice guidelines on management of oral and gastrointestinal mucosal injury 2015.[22]

ADDITIONAL INFORMATION

Soligenix Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 Clincaltrials.gov. *DOM-INNATE: Study of SGX942 for the Treatment of Oral Mucositis in Patients With Concomitant Chemoradiation Therapy for Head and Neck Cancer*. *Trial ID: NCT03237325*. Available from: https://clinicaltrials.gov/ct2/show/NCT03237325 [Accessed 18 May 2020].

2 Kudrimoti M, Curtis A, Azawi S, Worden F, Katz S, Adkins D, et al. Dusquetide: A novel innate defense regulator demonstrating a significant and consistent reduction in the duration of oral mucositis in preclinical data and a randomized, placebo-controlled phase 2a clinical study. *J Biotechnol*. 2016 Dec 10;239:115-25. Available from: https://doi.org/10.1016/j.jbiotec.2016.10.010.

3 Cision PN. *Soligenix Receives European Patent for Dusquetide and Related Innate Defense Regulator Analogs*. Available from: https://www.prnewswire.com/news-releases/soligenix-receives-european-patent-for-dusquetide-and-related-innate-defense-regulator-analogs-300782227.html [Accessed 18 May 2020].

4 Kudrimoti M, Curtis A, Azawi S, Worden F, Katz S, Adkins D, et al. Dusquetide: Reduction in oral mucositis associated with enduring ancillary benefits in tumor resolution and decreased mortality in head and neck cancer patients. *Biotechnol Rep (Amst)*. 2017 Sep;15:24-6. Available from: https://doi.org/10.1016/j.btre.2017.05.002.

5 CISION:PR Newswire. *Soligenix Announces SGX942 Receives Promising Innovative Medicine Designation from the UK Medicines and Healthcare Products Regulatory Agency*. Available from: https://www.prnewswire.com/news-releases/soligenix-announces-sgx942-receives-promising-innovative-medicine-designation-from-the-uk-medicines-and-healthcare-products-regulatory-agency-300376127.html [Accessed 17 June 2020].

6 Drugs.com. *FDA Grants Soligenix "Fast Track" Designation for SGX942 for the Treatment of Oral Mucositis in Patients with Head and Neck Cancer*. Available from: https://www.drugs.com/nda/sgx942_130603.html [Accessed 18 May 2020].

7 Nagi R, Patil DJ, Rakesh N, Jain S, Sahu S. Natural agents in the management of oral mucositis in cancer patients-systematic review. *J Oral Biol Craniofac Res*. 2018 Sep-Dec;8(3):245-54. Available from: https://doi.org/10.1016/j.jobcr.2017.12.003.

8 National Insitute for Health and Care Excellence. *Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy (IPG615)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ipg615/resources/lowlevel-laser-therapy-for-preventing-or-treating-oral-mucositis-caused-by-radiotherapy-or-chemotherapy-pdf-1899873923856325 [Accessed 18 May 2020].

9 Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer. *Neoplasia*. 2004 Sep-Oct;6(5):423-31. Available from: https://doi.org/10.1593/neo.04169.

10 Berger K, Schopohl D, Bollig A, Strobach D, Rieger C, Rublee D, et al. Burden of Oral Mucositis: A Systematic Review and Implications for Future Research. *Oncol Res Treat*. 2018;41(6):399-405. Available from: https://doi.org/10.1159/000487085.

11 Cancer Therapy Advisor. *Oral Mucositis: Chemotherapy-Associated Toxicity*. Available from: https://www.cancertherapyadvisor.com/home/cancer-topics/supportive-care/side-effect-management/oral-mucositis-chemotherapy-associated-toxicity/ [Accessed 18 June 2020].

12 Moslemi D, Nokhandani AM, Otaghsaraei MT, Moghadamnia Y, Kazemi S, Moghadamnia AA. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A

review of the current literature. *Radiotherapy and Oncology*. 2016;120(1):13-20. Available from: https://www.sciencedirect.com/science/article/pii/S0167814016310350?via%3Dihub.
13 National Cancer Registration and Analysis Service. *Chemotherapy, Radiotherapy and Tumour Resection by Tumour & Patient Characteristics in England, 2013 - 2015*. 2018. Available from: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/topic_specific_work/main_cancer_treatments [Accessed 18 May 2020].
14 Thomsen M, Vitetta L. Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. *Integr Cancer Ther*. 2018 Dec;17(4):1027-47. Available from: https://doi.org/10.1177/1534735418794885.
15 Shankar A, Roy S, Bhandari M, Rath GK, Biswas AS, Kanodia R, et al. Current Trends in Management of Oral Mucositis in Cancer Treatment. *Asian Pac J Cancer Prev*. 2017 Aug 27;18(8):2019-26. Available from: https://doi.org/10.22034/apjcp.2017.18.8.2019.
16 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 18/05/2020].
17 Chaveli-López B, Bagán-Sebastián JV. Treatment of oral mucositis due to chemotherapy. *Journal of clinical and experimental dentistry*. 2016;8(2):e201. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808317/.
18 National institute for Health and Care Excellence. *Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy* Last Update Date: Available from: https://www.nice.org.uk/guidance/ipg615/resources/lowlevel-laser-therapy-for-preventing-or-treating-oral-mucositis-caused-by-radiotherapy-or-chemotherapy-pdf-1899873923856325 [Accessed 18 May 2020].
19 Medicines Complete. *Mucositis (Antineoplastics - Treatment of Adverse Effects)*. Available from: https://www.medicinescomplete.com/#/content/martindale/1800-a2-1-h?hspl=oral&hspl=mucositis [Accessed 18 May 2020].
20 UK Oral Management in Cancer Care Group (UKOMiC). *Oral Care guidance and support in cancer and palliative care* Last Update Date: Available from: http://ukomic.co.uk/documents/UKOMiC-Guidelines-3rd-Edition.pdf [Accessed 18 May 2020].
21 The Royal College of Surgeons of England/ The British Society for Disability and Oral Health. *The Oral Management of Oncology Patients Requiring Radiotherapy, Chemotherapy and / or Bone Marrow Transplantation* Last Update Date: Available from: https://www.rcseng.ac.uk/-/media/files/rcs/fds/publications/rcs-oncology-guideline-update--v36.pdf [Accessed 18 May 2020].
22 Peterson DE, Committee obotEG, Boers-Doets CB, Committee obotEG, Bensadoun RJ, Committee obotEG, et al. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up†. *Annals of Oncology*. 2015;26(suppl_5):v139-v51. Available from: https://doi.org/10.1093/annonc/mdv202.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.