

## **PROTHELIAL™ (POLYMERIZED CROSS-LINKED HIGH POTENCY SUCRALFATE): MEDICAL DEVICE THERAPY FOR TREATMENT AND PREVENTION OF MUCOSITIS**

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### **ABSTRACT**

Effective management of mucositis in cancer patients permits oncologists to optimize treatment regimens, achieve superior outcomes and maximize survival. To date there has been limited therapeutic options available to oncologists for effective mucositis management. ProThelial™ polymerized cross-linked high potency sucralfate recently cleared by the U.S. Food and Drug Administration as a hydrogel medical device for the management (treatment and prevention) of oral mucositis. In contradistinction to other mucositis interventions, ProThelial™ has been associated with 2-3 day rapid reversal of oral mucositis, complete prevention of oral mucositis and reversal of small bowel and colonic mucositis. It is likely to substantially impact the management of oral mucositis in patients undergoing treatment for cancer.

**Keywords:** Sucralfate, Mucositis, ProThelial, Chemo-radiation induced, Polymerized Sucralfate.

### **INTRODUCTION**

Therapeutic dosing of radiation and anti-neoplastic drugs and biological treatments always lead to multiple side effects that can in turn limit dose-optimization and thereby survival in cancer treatment patients. Mucositis is one such side effect. As one of the more debilitating side effects of anti-neoplastic therapies, oral mucositis threatens therapeutic control of the neoplastic process, severely diminishes the patient's quality of life and increases the overall costs of cancer care.

Given the general uniformity in treatment approaches worldwide, the largely similar global prevalence of cancer, the annual incidence of oral mucositis resulting from chemotherapy and radiation is 400,000 per 316 million population [1] (if the U.S. is a measure) or 1,266 patients per million. When applied to the worldwide population of 7 billion, there may be as many as 8.9 million oral mucositis patients globally.

Among patients receiving myelo-suppressive cancer treatment therapies, 59.5% are affected by oral mucositis, 18.9% by gastrointestinal mucositis and 21.6% by both [2]. Of the 921,000 head neck patients under treatment worldwide, 91% develop mucositis, with 68% with either Grade 3 or 4, and

of the 115, 000 patients worldwide that undergo bone marrow transplants annually, nearly 100% develop oral mucositis.

Despite an industry-wide need of effective mucositis interventions, none to date rise to the challenge posed by mucositis, leaving clinicians with options that include mouth rinses and the off-label use of agents intended for other diseases [3, 4]. Such agents – antimicrobials, mucosal coating agents, anesthetics, amifostine and analgesics – have not altered the effect of mucositis on patients' ability to eat, swallow and drink. Novel uses of non-drug, externally applied physical agents such as laser [5] and cryotherapy [6] have yielded limited clinical success, but are burdensome for practical use. Disappointingly, interventions involving cytokines and growth factors have been either ineffective or of limited value owing to the restricted clinical setting appropriate for their use [7].

## MUCOSITIS

Underlying the ulceration of oral mucositis is a disorderly imbalance of pro-inflammatory and anti-inflammatory cytokines. Both, in coordination with other agents, are responsible for maintaining the integrity of the mucosa. However anti-neoplastic therapies – ionizing radiation, anti-metabolite chemotherapy, anti-tumor antibodies - damage cells, cellular membranes, which in turn provoke energetic responses to injury. Under physiologic conditions, immuno-modulatory elements, chiefly growth factors, are genetically tasked to govern and re-establish balance between pro-inflammatory and anti-inflammatory cytokines, with the goal of restoring normal mucosal integrity. In mucositis, persistent exposure to offending agents (chemo-radiation) makes elusive any return to normal mucosal integrity. The overall effect of growth factor in restoring cytokine balance is highly dependent on its synergy with other cellular elements, the membrane density of their targeted receptors and the tissue's response to their effort. In mucositis, all too often, the balance is never restored in a timely manner due to continued treatment, leaving patients with persisting mucosal damage. Unmitigated mucosal disruption impacts function (swallowing, salivation), which in turn immediately impacts quality of health, nutritional state and life in general. The mode of action for ProThelial™ centers on its physical effect on growth factors responsible for mucosal healing and on ion-gated nociceptors associated with mucosal pain.

### Grades of Mucositis

There are several scales used to assess the symptoms, severity and functional disturbance of mucositis, all of which use a grading system that range from Grade 0 to Grade 4. The World Health Organization, (WHO), and the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) are common scales used by clinicians and investigators (Table 1).

Between Grade 0 and Grade 1, there are diminutive disruptions within the epithelial lining beginning early in the course of antineoplastic therapy marked by symptomless reparative secretion of pro-inflammatory cytokines within the mucosa. During this period there is feedback secretion of anti-inflammatory cytokines and growth factor as well as an increased expression of growth factor

receptor sites [8-11]. This marks the beginning of mucositis. Grade 1 mucositis is generally experienced by the patient as sharp burning discomfort associated with a normal-appearing mucosal lining. This is likely due to an elevated concentration of pro-inflammatory cytokines and their effect on sensory neurons embedded within the mucosa. Grades 2, 3 and 4 are escalating levels of symptomatic and histologic dysfunction that result in a compromised ability to eat, drink and maintain a baseline nutritional state. Serum elevations of certain pro-inflammatory cytokines contribute to the “sickness syndrome” often exhibited by patients with mucositis [12].

### **Mucositis: A Disruption of Epithelial Homeostasis**

Therapeutic use of either of the three anti-neoplastic treatments - radiation, chemotherapy and biologicals - result in mucositis via disruption of the ‘homeostatic mechanism’ genetically tasked to maintain normative histologic states in epithelial linings. This “homeostatic mechanism” consists of pro-inflammatory cytokines held in balance with anti-inflammatory cytokines, a balance that is genetically governed by a baseline secretion of growth factor and the constitutive expression of growth factor receptor sites [13]. Disruption of this balance always results in the loss of epithelial integrity.

### **Three Anti-neoplastic Pathways to Mucositis**

Radiation therapy produces intracellular ionized radicals [14] that cause membrane disruption, accelerated cell death inciting an exaggerated elevation of pro-inflammatory cytokines secreted in attempt to address cellular debris caused by radiation. Traditional chemotherapies are metabolic toxins that cause accelerated cellular death [14], membrane disruption and a requisite secretion of pro-inflammatory cytokines to address the resultant cellular debris. Anti-neoplastic biologicals that target either growth factor or markers of the growth factor receptor site, lead to mucositis by crippling epithelium’s ability to genetically govern the balance between pro-inflammatory and anti-inflammatory cytokines, which also leads to cellular destruction, membrane disruption and enhanced secretion of pro-inflammatory cytokines [15]. Though enhanced pro-inflammatory cytokine secretion cause obligatory feedback secretion of anti-inflammatory cytokines, including enhanced secretion of growth factor and enhanced expression of growth factor receptor sites [16], this feedback is not sufficient to restore balance. Thus, as long as exposure to the inciting agent continues, mucositis persists, and worsens in clinical grades as the imbalance of ‘cytokine-to-growth factor-to-growth factor receptor site’ sinks to ever-lowering levels of stalemate.

### **Duration of Mucositis**

Clinically significant mucositis interferes with daily activities of eating, drinking, and sleeping and is associated with depressed quality of life outcomes. It is difficult to find a single reference detailing patient-reported duration of clinical mucositis in context of the multiple treatment scenarios. Indeed, the clinical duration of mucositis is not as short as one would be led to believe from an often-repeated refrain of mucositis being self-limited, healing within 2 to 4 weeks following the cessation of chemo-radiation if not complicated by infection. [17].

**Table 1. EORTCRTOG & WHO Toxicity Criteria Acute Chemo-Radiation Morbidity**

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<b>Oral &amp; GI Toxicity Scale</b>					
<b>WHO Oral Mucosal Toxicity Grade</b>	None	Painless ulcers, erythema or mild soreness with swallowing liquid, hard & soft solids	Painful erythema, edema, or ulcers but can eat only soft solids & liquids	Painful erythema, edema, or ulcers and cannot eat solids, barely drink liquids	Allimentation is not possible; Dependence on IV & Feeding-Tube
<b>EORTCRTOG Esophagus Toxicity Grade</b>	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula
<b>EORTCRTOG Small Bowel Toxicity Grade</b>	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily	Moderate diarrhea and colic; Bowel movement >5 times daily;	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula
<b>EORTCRTOG Colorectal Toxicity Grade</b>	None	Increased frequency or change in quality of bowel habits not requiring medication, rectal discomfort not requiring analgesics; Slight rectal discharge or bleeding	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics; Excessive rectal mucus or intermittent bleeding	Diarrhea requiring parenteral support, severe mucous or bloody discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
<b>WHO Colorectal Toxicity Grade</b>	None	Increase of 2-3 stools per d over pretreatment	Increase of 4-6 stools per d, or nocturnal stools, or moderate cramping	Increase of 7-9 stools per d, or incontinence, or severe cramping	Increase of >10 stools per d or grossly bloody diarrhea, or need for parenteral support
<b>EORTC/RTOG is the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group ; WHO is the World Health Organization</b>					

Antimicrobials neither shorten the course, nor lessen the severity of mucositis [3]. Therefore local infection is not a driver of mucositis. Since the “two-to-four week, self-limited” nature of mucositis follows many weeks of daily radiotherapy or multiple cycles of chemotherapy, the patient-reported duration of clinically relevant mucositis is not short.

There are three treatment scenarios associated with the development of mucositis – (a) myeloablative conditioning in hematopoietic stem-cell transplant (HSCT) accounting for 1.6% of oral mucositis patients, (b) radiation with and without chemotherapy, accounting for 13.8% and (c) multi-cycle chemotherapy, accounting for 84.6% of all oral mucositis patients.

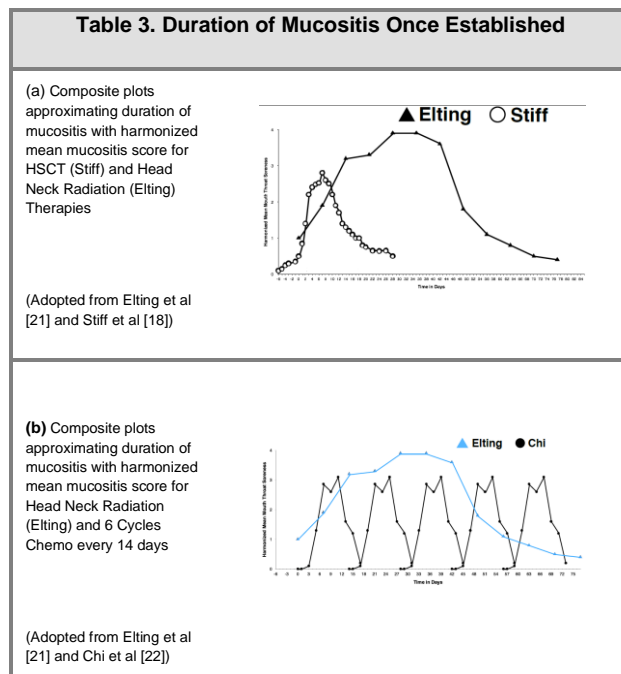
**Table. 2** Days of Clinically Significant Oral Mucositis and Percent of Mucositis Patients Affected Annually

Therapy	Days of Mucositis	Percent Oral Mucositis Patients	Reference
Myeloablative Therapy HSCT	46-60 days	1.6%	Stiff et al [18] ; Kushner et al [19]
Radiation ± Chemotherapy	84-106days	13.8%	Elting et al [2,20,21]
Multiple Cycle Chemotherapy	68 -102 days	84.6%	Chi et al [22]

The time interval for symptomatic mucositis is dependent on the period of exposure to the inciting agent (see **Table 2**). Patients undergoing bone marrow transplants typically receive a single myeloablative dose of radiation and chemotherapy; their experience of mucositis peaks at 7 days, trails out to 30 days and returns to baseline by 46 days [18]. By another account [19] mucositis symptoms in these patients can extend to 60 days.

Patients under the standard six-week treatment of radiation with or without chemotherapy for head and neck cancer experience clinically significant mucositis for 60 to 70 days, returning to baseline between 84 to 91 days [20-21].

Patients receiving chemotherapy will experience mucositis over a period of 17 days per cycle. Given that most regimens require four to six cycles, there can be 68 to 102 days of clinical mucositis in patients receiving chemotherapy [22]. Patients receiving multiple cycles of chemotherapy who develop mucositis will experience an escalation of pain intensity as high as 44% in successive cycles [22].



Harmonizing data points in terms of a mean mucositis score over a period of 84 days (**Table 3**), provides context on the duration of clinically symptomatic mucositis.

Two of three treatment scenarios [**18, 21**] in **Table 3(a)** show that mucositis lasts far longer than two to four weeks following cessation of treatment. Though following a single cycle of chemotherapy, symptomatic mucositis may be substantially ended in 17 days, four to six cycles of chemotherapy shown in **Table 3(b)** assures 68 to 102 days of mucositis. By far the longest periods of mucositis experienced are in patients receiving combined chemo-radiation where symptoms can persist beyond 80 days, while the shortest period is among patients receiving myeloablative therapy for HSCT with symptoms that extrapolate to 46 days.

A therapeutic intervention that disrupts the course mucositis or prevents it altogether would represent a major advancement in supportive care, and a positive change in clinical practice.

### **Current FDA-Cleared Devices and Therapies**

Devices and therapies currently cleared by the FDA for the management of mucositis include oral rinses - MuGard®, Caphosol®, Gelclair® and Episil®. ‘Magic Mouthwash’ is a widely known, pharmacist-formulated rinse containing diphenhydramine, hydrocortisone, nystatin powder, aluminum/magnesium hydroxide and tetracycline. The therapeutic thrust of these agents is palliation, lessening the discomfort of mucositis rather than eliminating the pain or the need for narcotic analgesia.

A recent randomized controlled trial on one of these agents summarized what could be considered the collective reality of each agent: “*Despite MuGard’s efficacy in attenuating MTS (mouth throat soreness), it was not superior to control (placebo) in impacting subjects’ ability to swallow, eat, or drink. Nor did MuGard significantly alter gastrostomy reliance, unplanned office visits, emergency room visits or hospitalizations*” due to mucositis [**23**]. The limited efficacies of these agents fail to offer benefit significant enough to be adopted into clinical practice by oncologists.

Keratinocyte (epithelial) growth factor (Kepivance®) is a therapeutic option designed to address the presumed lack of restorative action of growth factor in the ulcerative lesions of mucositis. Though successful in altering the incidence of severe (Grades 3,4) mucositis, it lacks significant efficacy for Grades 1 and 2, it does not eliminate pain and it is limited to use in bone marrow transplant patients, which is less than 2% of those prone to mucositis. Thus, given these ineffectual therapeutic options, chemo-radiation induced mucositis remains an unmet medical need.

### **PROTHELIAL™ MEDICAL DEVICE**

Mueller Medical International LLC (Storrs, Connecticut USA) developed ProThelial™ for the management of mucosal ulcerations of the oral cavity that occurs due to chemo-radiation. Since its release to market, ProThelial™ has been associated with rapid reversal and complete prevention of mucositis due to chemotherapy and radiation. The following covers its description, licensed

indication, prescribed method of use, basic technology, mechanism of action, pre-market and post-market surveillance data, efficacy and pediatric use.

### Description and Licensed Indication

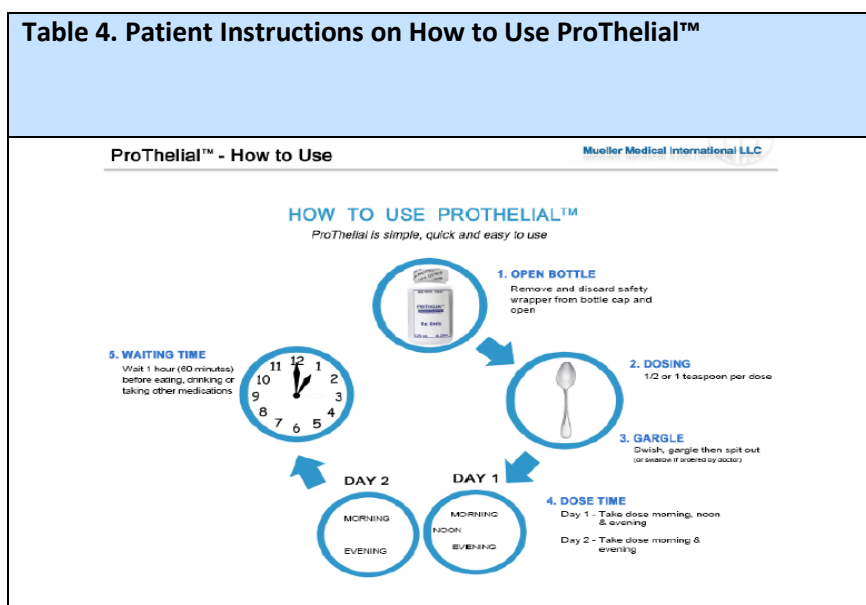
ProThelial™ is an advanced formulation of sucralfate rendered as a yogurt-like paste, FDA cleared for the management of oral mucositis. It forms a protective layer over the oral mucosa by adhering to the mucosal surface, which allows it to protect against further irritation, relieve pain and facilitate healing. The paste may be used in the management (treatment and prevention) of mouth lesions of all types, including aphthous ulcers, stomatitis and mucositis.

### Prescribed Method of Use

The FDA-cleared quantity of sucralfate in each dose of ProThelial™ is 250mg to 500mg to be used three times daily for the first day, followed by the same amount used twice daily. Each dose is swirled in mouth, gargled and then expectorated.

### Higher Adjusted Dosing

Post-market surveillance studies have shown that some patients require 1,000mg of ProThelial or 10ml (two teaspoons) per dose or more for desired effect of pain elimination and ulceration reversal. Among those requiring higher adjusted doses are patients who were smokers up to 6 months prior to cancer treatment.





### Swallowing ProThelial™

As a medical device, ProThelial™ is intended for oral use only. However many oncologists in post-market surveillance are instructing patients to swallow ProThelial™ rather than expectorate it, so as to achieve clinical benefit for the esophagus and distal GI tract. The FDA required it be stated in its package insert that ProThelial™ is safe if swallowed in doses up to 4 grams daily for 56 days. This of course is the customary FDA-approved dosing of standard non-polymerized, non-cross-linked sucralfate -1,000mg- which is swallowed four times daily. It is safe to swallow ProThelial™, and, in some patients as found by oncologists, it may be preferred. Licensed instructions regarding the use of ProThelial™ are straightforward and are shown in **Table 4**.

**Table 5. Comparing Standard Sucralfate to Polymerized Cross-Linked Sucralfate**

Standard Potency Sucralfate	High Potency Sucralfate	
	Polymerized Sucralfate	Cross-Linked Sucralfate
<ul style="list-style-type: none"> <li>Hydrated Singular Sucralfate</li> <li>Singular Sucralfate Molecules mostly suspended in solution</li> <li>Minimal Amount of Sucralfate available for coating mucosa</li> </ul>	<ul style="list-style-type: none"> <li>Sheets of Sucralfate Hydrogen Bonded</li> <li>By Multi-dentate Chelators (edta, oxalate, malate, citrate)</li> <li>As Sheets of Sucralfate there is less singular hydrated sucralfate in solution and more sucralfate is available for layering.</li> <li>More complete Mucosal Coating</li> </ul>	<ul style="list-style-type: none"> <li>Sheets are Cross-Linked</li> <li>Cross-linking via bivalent, trivalent Cations (Fe, Mg, Ca,)</li> <li>Pi-stacking of Sucralfate Sheets fastening layer by layer</li> <li>3 hours following dosing there is                             <ul style="list-style-type: none"> <li>7 fold Greater coating on normal lining</li> <li>23 fold greater coating on ulcerated lining</li> </ul> </li> </ul>

ProThelial™ contains polymerized cross-linked sucralfate, which differentiates it from standard sucralfate, in that ProThelial™ achieves amplified concentration on the mucosal lining. Given that the entirety of sucralfate potency is restricted to its topical association with the mucosal lining, sucralfate within ProThelial™ has been referred to as high potency, because it achieves and maintains augmented concentrations of sucralfate on the mucosal lining.

### High Potency Polymerized Cross-Linked Sucralfate

ProThelial™ contains polymerized cross-linked sucralfate, or PCLS, which is standard sucralfate reformulated by polymerization with malic acid then cross-linked by calcium-chelation (**Table 5**). The exact configuration of sucralfate in PCLS is not known, but it is believed that singular



molecular sucralfate is polymerized by malate into ‘sheets of sucralfate’ that are in turn cross-linked by calcium that is partially chelated by malate. ‘Cross-linking’ electronegative ‘sheets of sucralfate’ in a ‘pancake’ fashion lead to an orderly, compounded layering of sucralfate on the mucosal lining, a process known as (pi)  $\pi$ -stacking [24, 25]. When standard formulations of sucralfate (tablets, suspensions or paste) are dissolved, the majority of singular molecules of sucralfate remain hydrated with very little to adhere to the lining - most of it having been dissolved in the luminal contents.

Parallel  $\pi$ -stacking of sucralfate in ProThelial™, however, disallows single molecules of sucralfate to participate in random positioning on the lining or free dispersal by hydration. Instead, in PCLS, sucralfate that is polymerized into sheets is also cross-linked, resulting in preferential layering of ‘sucralfate sheets’ upon each other, thereby increasing the surface concentration of sucralfate upon the mucosal lining throughout the gastrointestinal tract.

Three hours following dose administration of ProThelial™, sucralfate maintains an increased concentration 800% greater than usual on normal lining and 2,400% greater on ulcerated lining [26].

### **Mechanism of Action**

ProThelial™ has a device mechanism of action that leads to expedited healing and alleviation of pain. Since mucosa-embedded nociceptors for nausea and cramping utilize ion-gated switches to turn receptors on or off, the device mechanism of action of ProThelial™ aids in the reversal of these symptoms as well.

### **Device Mechanism of Action of ProThelial™: Expedited Growth-factor Mediated Healing**

The more efficient compounded layering of polymerized sucralfate paste produces an adherent restrictive micro-environment applied across the mucosal lining. Transiently fixed microenviroins created by adherent PCLS facilitate the activation of growth factor receptors by growth factor. Restrictive micro-enviroins fashioned by cross-linked layers of polymerized sucralfate “crowds” free-moving growth factor, limiting its random movements to “sucralfate-pockets” that overlie growth factor receptors. Spatially limiting the movement of growth factor to the vicinity of its receptor heightens the chances of receptor site activation. This device action leads to expedited healing.

### **‘Bulk’ Sucralfate Causing Expedited Healing**

Undissolved fragments –bulk sucralfate - sitting upon the gastric wall present a high dosage of concentrated sucralfate to the mucosa. Early studies on the mucosal reaction to contact by bulk, undissolved fragments of sucralfate demonstrated near immediate (within 10 minutes) regenerative changes of healing in the epithelium [27-28]. It was suspected that these rapid sucralfate-mediated mucosal changes were growth factor dependent [29-30]. Indeed, these regenerative changes of healing were shown to be linked to a local increased expression of growth factor receptors [32-33] and to a focal increased secretion of epidermal growth factor [13, 34] in the absence of sucralfate.

Konturek et al concluded that the physical presence of sucralfate on the mucosal lining accelerates growth-factor mediated mucosal healing [35].

### **Device Mechanism of Action for PCLS – Reversing Mucosal-Based Pain, Nausea & Diarrhea**

Depending on its site in the GI tract, mucositis irritation leads to pain, nausea, crampiness, vomiting and diarrhea. Often the mucosal receptors associated with these symptoms are voltage or ion-gated receptors [36] turning on with the flux of ion exchange across a depolarized membrane, turning off

with the ion flux stops. The surface “pockets” of restrictive micro-environs created by PCLS’s unique layering can affect the flux of ions across mucosal receptors responsible for pain, nausea, vomiting and neuro-secretory diarrhea (often cytokine-mediated) [37-38]. These specialized mucosal receptors triggered by chemo-radiation-induced cytokines maintain their state of activation by means of gated-ion fluxes across surface membranes facing the lumen of the gut. It is hypothesized that the restrictive micro-environs created by PCLS that crowd growth factors to the vicinity of their receptors also affect the surrounding space available to membranes for ion-flux and exchange. Enhanced mucoadherent PCLS on the mucosa of the oral cavity (and along the GI tract) imposes a spatial limitation of the immediate surface environment surrounding ion-gated receptors; this impacts the receptor’s ability to perpetuate the ion fluxes required to keep the receptor “turned on” or stimulated. Physically restrictive micro-environs surrounding membranes of stimulated receptors exhaust the ions immediately available to it, limiting the ability of the receptor to stay “on”. The result is a quiescence of the membrane flux and the reduction of receptor-associated pain, nausea (thereby vomiting) and neurosecretory diarrhea, all of which had been triggered by chemo-radiation therapy.

### **Clinical Experience with ProThelial™**

Clinical experience with ProThelial™ has been defined by the clinical outcomes in observational data. The pre-market experience consists of a single patient with Stage 4 locally metastatic squamous cell carcinoma of the head and neck while the post-market surveillance consists of a 32-patient mucositis registry reported at a recent symposium of the Multinational Association of Supportive Cancer Care (MASCC) [39]. In each instance, before and after FDA clearance, ProThelial™ outperformed expectations by either rapidly reversing mucositis in the oral cavity, esophagus, small bowel and colon as well as preventing mucositis in high-risk patients. Despite the lack of randomized controlled trials, a positive Glasziou treatment effect [40] confirms the efficacy of ProThelial™. The general 60- to 84-day duration of oral mucositis was either entirely prevented, that is reduced to zero days or rapidly reversed in 2-3 days, wherein ulcerated mucosa reverted to normal. These observations have not been seen with any other mucositis intervention – device, drug or physical remedy (laser, cryotherapy).

### **Pre-Market Experience – Rapid Reversal of Oral and Alimentary Mucositis**

The use of PCLS (ProThelial™) prior to market clearance by the FDA involved a single patient with advanced locally metastatic squamous cell carcinoma of the oral cavity (tonsils). Reported previously [41] a 43 year old male with advanced head and neck squamous cell carcinoma requiring

concurrent chemo-radiation comprised 6 weekly infusions of paclitaxel and carboplatin with radiation totaling 201Gy (71Gy for base of tongue, 71Gy to the tumor mass with an additional radiation dose of 59Gy to regional nodes). Since he was at risk for the worst form of mucositis which generally lasts 84 to 91 days [21], he received a prophylactic gastrostomy tube for anticipated inability to swallow, requiring artificial tube feeding to survive. Two weeks into chemo-radiation, he had developed Grade 2 oral mucositis and Grade 2 alimentary mucositis with dysgeusia and xerostomia. One-and-a-half gram (1.5gm) doses of PCLS (ProThelial™) in suspension form was swished and swallowed three times daily for 2 d, then twice daily. [This administration differed due to the anticipated severity of mucositis]. All symptoms and signs of mucositis cleared in 2 to 3 days.

### **Patient-Initiated Non-compliance**

The patient inadvertently discontinued PCLS (ProThelial™) by the end of week 4 during chemo-radiation cancer treatment. Four days later, both oral (Grade 2) and gastrointestinal mucositis (Grade 2) returned, prompting resumption of PCLS. Without a loading regimen, patient resumed PCLS using 1.5 grams to swish and swallow twice daily. Both OM and GIM resolved within 2 days. At no time during therapy did the patient require use of a feeding tube. The patient continued PCLS for two weeks beyond the course of cancer treatment with no adverse reactions to PCLS (ProThelial™).

### **Key Points of the Pre-market Experience**

The key points of this early pre-market experience were that ProThelial™ (1) rapidly reversed mucositis, (2) prevented mucositis from occurring while using it, and (3) demonstrated clinical effect in both oral and gastrointestinal mucositis. Oral mucositis lesions and tenderness completely disappeared along with patient-reported disappearance of pain, nausea and diarrhea. Despite continued high-dose radiation, concurrent weekly cycles of carboplatin and paclitaxel, the patient did not develop mucositis, did not require opiate analgesia and did not require tube-feeding supplements to a regular oral diet while on ProThelial™.

### **Post-Market Experience - Rapid Reversal of Oral and Alimentary Mucositis**

To conduct a Phase IV post-market surveillance of ProThelial™, a mucositis registry was established to monitor any unanticipated adverse reactions. Patients with mucositis or who were vulnerable to develop mucositis were identified by their oncologists and prescribed one week samples of ProThelial™ on a weekly basis. Enrollment in the registry was open, with no exclusion criteria as to the type of cancer treatment or the type and stage of cancer.

### **Registry Patients and the Prescribing Oncologists**

Of the 32 unique patients in the registry (**Table 6**) presented at the MASCC Symposium [39], there were 11 females and 21 males with an average age of 62.5 (+/- 13.8). The age for men was 60.5 (+/- 14.3) and age for women was 67.3 (+/- 12.2). Twenty-one unique oncologists were involved. Ten radiation oncologists (n=10) prescribed weekly ProThelial™ samples to 19 patients and 11 medical oncologists prescribed to ProThelial™ to 13 patients.

### **Registry Clinical Setting for Patients, Cancer Types and Treatments**

The registry was a multi-center log with the majority of patients having community-based oncologists (n = 25), while a minority of patients had oncologists based in tertiary care academic centers (n = 7). Nineteen patients were under treatment (n=19) for squamous cell carcinoma of the head and neck (SCCHN). Of the 13 non-SCCHN patients, five (n=5) had no diagnosis provided, two (n = 2) had lymphoma, two (n = 2) had colon cancer, one each had pancreatic cancer (n = 1), esophageal cancer (n = 1), melanoma (n = 1) and soft-tissue sarcoma (n = 1). Of the 27 patients with complete treatment information, ten patients (n = 10) received radiation alone, seven patients (n=7) received chemotherapy alone and seven (n=7) received combined chemo-radiation. Chemotherapy agents included paclitaxel, carboplatin, ipilimumab, nivolumab, folfirinox, folfox, folfin, cetuximab, rituximab, bevacixumab and pazopanib.

**Table 6. Mucositis Patient Registry for ProThelial™ Polymerized Cross Linked Sucralfate – A Post Market Surveillance**

Unique Patient	Age Gender	Clinical Institution	Cancer	Radiation	Chemotherapy	Oral Mucositis	Gastrointestinal Mucositis	Reversed Ulceration	Reversed Painful Swallowing	Reversed Nausea, Cramps	Reversed Diarrhea
<b>1</b>	43yoM	1,2	SCCHN	YES	Paclitaxel Carboplatin	Grade 2	Grade 2	1 day	1 day	----	1day
<b>2</b>	48yoF	3,4	Metastatic Melanoma	NO	Ipilimumab Nivolumab	Grade 3	Grade 3	2 days	2 days	2 days	2 days
<b>3</b>	56yoM	5	SCCHN	YES	NO	Grade 3	---	3 days	3 days	--	--
<b>4</b>	68yoF	6	■	NO	YES	■	■	■	■	■	■
<b>5</b>	F	7	■	NO	YES	■	■	■	■	■	■
<b>6</b>	F	7	■	NO	YES	■	■	■	■	■	■
<b>7</b>	F	8	■	NO	YES	■	■	■	■	■	■
<b>8</b>	F	8	■	NO	YES	■	■	■	■	■	■
<b>9</b>	68yoF	9	SCCHN tongue	YES	NO	Grade 2	---	2 days	2 days	---	---
<b>10</b>	59yoF	10	Esophageal Cancer	YES	YES	Grade 2	---	2 days	2 days	---	---
<b>11</b>	48yoM	11	Pancreatic Carcinoma	NO	Folfirinox	Grade 3	Grade 3	3 days	3 days	2 days	2 days
<b>12</b>	49yoM	12	SCCHN	YES	Cetuximab	Grade 3	Grade 2	2 days	3 days	1 days	1 day
<b>13</b>	64yoF	11	Metastatic Colon Ca	NO	Folfox	Grade 3	Grade 4	2 days	1 day	2 days	2 days
<b>14</b>	49yoM	11	SCCHN Tonsil	YES	YES	Grade 2	---	2 days	2 days	---	---
<b>15</b>	65yoM	11	Stage IV Colon Canc	NO	Folfin + Bevacizumab	Grade 2	Grade 2	2 days	2 days	2 days	2 days
<b>16</b>	80yoF	13	Soft Tissue Sarcoma	NO	Pazopanib	Grade 2	Grade 3	2 days	2 days	2 days	2 days

### **Registry Grade and Type of Mucositis**

There were no patients who had oral mucositis alone without difficulty swallowing and there were no patients who had gastrointestinal mucositis alone. At the time that ProThelial™ was prescribed, there were 19 patients who had active oropharyngeal mucositis with or without gastrointestinal involvement. Fourteen had Grade 2 (n=14) and five had Grade 3 (n=5) mucositis. There were 11 patients with gastrointestinal mucositis; one had Grade 1 (n=1), four had Grade 2 (n=4), five had Grade 3 (n=5) and one had Grade 4 (n=1).

### **Registry Outcomes on ProThelial™: Rapid Reversal and Complete Prevention**

Patients responded to ProThelial™ by either having a complete reversal of mucositis symptoms and signs (n=19), or the complete prevention of mucositis (n=8). All symptoms of mucositis resolved rapidly, generally within 1-3 days: (a) difficulty swallowing resolved in 1 day for three patients (n=3), in 2 days for eleven patients (n=11) and in 3 days in three patients (n=3); (b) small bowel mucositis symptoms of delayed nausea and cramps resolved in 1 day for two patients (n=2) and 2 days for eight patients (n=8); and (c) colonic diarrhea, or chemo-induced diarrhea, resolved in 1 day for two patients (n=2), in 2 days for six patients (n=6) and in 3 days in two patients (n=2).

### **ProThelial™ Averting the Prophylactic Implantation of Gastrostomy Feeding Tubes**

ProThelial™ prevented the onset of oral mucositis in several patients (n=8) with tonsillar or oral head and neck cancer who were anticipated to develop the most severe form (Grade 3, 4) of radiation-induced mucositis. These patients did not undergo the customary implantation of a gastrostomy tube because of the efficacy of ProThelial™ in preventing the onset of mucositis.

### **Elderly Patients with Mucositis**

While the elderly have similar survival rates as their younger cohort, they require more supportive care as they experience worse toxicity [42]. In this post-market experience with ProThelial™, there were 12 elderly patients age 65 years or older, eight of whom had active mucositis (n=8) and four were anticipated to develop mucositis (n=4). In all of these patients, mucositis was either rapidly reversed or completely prevented by ProThelial™. The time for mucositis reversal in the elderly was the same as that in younger patients.

### **Adverse Reactions to ProThelial™**

There were no adverse reactions to ProThelial™ and all patients found the intervention to be palatable.

### **Efficacy of ProThelial™: Glasziou Treatment Effect - Rate Ratio of ProThelial™ Compared to Current Interventions**

Though no randomized controlled trials have been conducted on ProThelial™ to date, efficacy has been established by the repeated demonstration of a positive Glasziou treatment effect compared to

either placebo, the natural course of the disorder, or to current mucositis interventions. Glasziou et al [40] explained the statistical significance of comparing rate ratios of interventions to placebo or the natural course of a disease. Namely that if the rate in which a treatment effect occurs through use of an intervention is less than 1/10 the rate seen or expected from placebo, other interventions or the natural course of the disease, then the treatment effect of that intervention is statistically beyond chance or any biases commonly minimized by randomized controlled trials. In other words, efficacy is assured if the magnitude of clinical effect from an intervention is 10 or more times greater than placebo or the natural course of disease, or 1100% greater.

### **ProThelial™ Shortening the Natural Course of Mucositis**

There are no interventions for oral or gastrointestinal (GI) mucositis that affect a complete treatment response – that is complete reversal of mucositis, its pain, erosions and ulcers with a corresponding restoration of enteral function. As discussed earlier, the natural course and duration of oral mucositis during chemo-radiation is 84 to 91 days [21] before patients return to baseline. The natural course of oral mucositis for patients undergoing stem cell transplant is 46 to 60 days [18-19]. Though the single cycle duration of mucositis for chemotherapy alone may be 17 days [22], the natural course of oral mucositis experienced by this patient population is 17 days multiplied by 4 to 6 cycles or 68 to 102 days.

### **Glasziou Treatment Effect Calculation**

In all treatment cases in the mucositis registry in the post-market surveillance, the rate of complete response of oral mucositis (pain, erosion, and function restoration) to ProThelial™ was 2-3 days, or 2.5 days. This is compared to 46, 60, 84 or 102 days expected for the natural course of chemo-radiation induced oral mucositis. As explained by Glasziou et al, the rate ratio in these situations would be calculated as follows.

$$\text{Rate for ProThelial} \div [0.5 \div \text{days for mucositis to naturally clear}] = \text{Rate Ratio} \\ [1 \div 2.5 \text{ days}] \div [0.5 \div 46, 60, 84 \text{ or } 102 \text{ days}] = 36.7, 48.2, 67.8 \text{ or } 81.6$$

The magnitude of the clinical response to ProThelial™ in post-market surveillance compared to the natural course of mucositis generated rate ratios that far exceeded the figure – ‘10’- required to secure assumption of efficacy beyond confounding biases. The magnitude of clinical response associated with ProThelial™ generated rate ratios of 37, 48, 68 or 82 depending on the anticipated duration of mucositis. These ratios mean that clinical effect of ProThelial™ was 3,700% to 8,200% greater than placebo or the natural course of mucositis disorder. This is significant given that other interventions in randomized controlled trials (Kepivance®, MuGard®, Gelclair®, Caphosol®) were only 20-50 basis points (or less than 200%) better than placebo in their primary outcome measures. Neither of the interventions have ever had a magnitude of clinical effect as ProThelial™, 3,700 to 8,200 basis points greater than placebo against mucositis.



## Key Points of the Post-market Experience

There were several key points of the post-market experience of ProThelial™, most of which are novel for a mucositis intervention.

- (1) **ProThelial™ rapidly reversed oral mucositis.** This is an unprecedented clinical effect, not associated with any other mucositis intervention.
- (2) **ProThelial™ prevented oral mucositis from occurring.** This is a clinical effect unequalled by any other mucositis intervention, device or drug.
- (3) **ProThelial™ averted the need for gastrostomy tube placement.** The prophylactic placement of gastrostomy tubes has become a “best-practice” approach in the care of patients with known head and neck cancer of the oral cavity and larynx as well as that requiring high dose chemotherapy [43]. It has been proven to benefit nutritional and caloric support, weight maintenance and improved quality of life in this patient population [44]. The use of ProThelial™ prevented mucositis sufficient enough to avert the need of gastrostomy tube placement. This clinical outcome is new for a mucositis intervention.
- (4) **ProThelial™ was safe when consistently swallowed.** This was not unexpected as sucralfate-based products have always been safe to swallow.
- (5) **ProThelial™ demonstrated clinical efficacy in both oral and gastrointestinal mucositis.** This is yet another first, as no other mucositis intervention has shown efficacy in oral, upper and lower gastrointestinal mucositis.
- (7) **ProThelial™ was equally effective in elderly as well as non-elderly patients.** This population can be more vulnerable in developing mucositis and more at risk in terms of survival as a result [42]. ProThelial™ was found to be a benefit.
- (8) **ProThelial™ required higher adjusted dosing in some.** Some patients required a higher 1000mg dose versus 250mg to 500mg for a mucositis-free experience of cancer treatment.
- (9) **ProThelial™ was not associated with any adverse events.** No adverse reactions were reported with the use of ProThelial™.

Despite continued high dose radiation with concomitant use of traditional chemotherapy and anti-neoplastic biologics, ProThelial™ reversed mucositis when it occurred, prevented it from occurring, averted the use of prophylactic gastrostomy tubes and permitted patients to have a mucositis-free experience, obviating dose reductions while maintaining normal nutritional intake.

## Pediatric Use of ProThelial™

Pediatric patients receiving chemo-radiation are particularly vulnerable to oral mucositis, with up to 80% on chemotherapy developing some grade of mucositis [45]. ProThelial™ was designed for use in the pediatric and adult patient population as is evident in its FDA 510(k) Summary [46]. Therefore, the use of ProThelial™ in pediatric patients is safe when the product is expectorated. With regard to swallowing, if the pediatric patient has normal renal function swallowing ProThelial™ at doses up to 0.75mg/kg per dose four times daily is likely safe for short periods (4-6 weeks per year).

While there have been no studies in the pediatric mucositis patient swallowing ProThelial™, the use of standard potency sucralfate swallowed at much higher doses has been studied in children with chemotherapy-induced mucositis [47]. Of the 48 patients in the trial 24 received sucralfate suspension, four times daily at a dose of 0.75mg/kg. In that trial, 58% of patients on sucralfate versus 25% of patients on placebo reported no pain and no adverse reactions or side effects were observed.

The swallowing of sucralfate-based products in the pediatric population has been reported in investigations that were focused on chronic use conditions [47 - 58], which differs from chemotherapy-induced mucositis, which involves transitory periodic use of sucralfate. Regarding the safety of swallowed sucralfate, there have been 12 studies involving 858 children, age 1 month to 16.5 years of age, randomized into controlled groups with 426 patients ingesting sucralfate. No adverse reactions or side effects from sucralfate were reported [47-58]. Doses of sucralfate varied according to weight and age, with children age 14 years and older receiving adult doses of 1 gram four times daily, while younger patients were dosed at 0.75mg/kg per dose four times daily.

Unless the patient is allergic to any of its ingredients or has a known previous adverse reaction to sucralfate, the transitory episodic use of ProThelial™ in pediatric patients with mucositis is safe if it is expectorated.

Clinical caution as mentioned above should be used if ProThelial™ is to be swallowed by mucositis patients under the age of 14.

### **Health Economics and Outcome Costs of Mucositis**

The costs of mucositis are high. Largely ineffective for many patients, standard mucositis treatments rarely help patients avoid dehydration, which often require ER visits and/or hospitalizations [59-62]. By the estimate of one report [62] oral and gastrointestinal mucositis was the leading cause of visits to the ER. Of the 91,561 patients studied in one investigation, 3,525 complained of nausea and vomiting, 3,146 had dehydration and 4,972 complained of malaise and fatigue for a total of 11,643 or 12.7%. The next-nearest cause of ER visits was abdominal pain at 4.7%.

Poorly managed mucositis creates a substantial economic burden in cancer care [2]. Patients receiving an average of 6 cycles of chemotherapy for solid tumors or lymphoma-generate additional costs of \$2,384 per cycle for oral mucositis and \$5,239 per cycle when both oral mucositis and gastrointestinal mucositis are involved [2]. Thus the overall costs associated with poorly managed mucositis arising from chemotherapy alone range from \$14,304 to \$31,434 per patient per treatment. Patients receiving radiation treatment alone or with chemotherapy require additional costs of \$14,646 to \$28,660 [21]. For a patient undergoing a bone marrow transplant oral mucositis and gastrointestinal mucositis impose additional costs of \$42,747 [63].

**TABLE 7. Comparative Product Ingredients & Treatment Mechanism**

Product	FDA Registration	NDC	Active Ingredients	Mechanism of Treatment
ProThelial™	510k 123904	P-Pak 500 33801-125-04 33801-250-02 33801-210-21	Polymerized Cross-linked Sucralfate	Polymerized sucralfate sheets are cross-linked to each other layer by layer resulting in 23 fold more muco-adherent than generic sucralfate 3 hours after dose, used 2 times daily or as needed, eliminate ulcers, prevent ulcers, and eliminate pain.
Episil®	510k 101769	53270-0100-10	Glycerol dioleate, Soy Phosphatidyl Choline, Peppermint oil	Chemical mouth rinse intended to mimic mucosal membrane for pain reduction; used 3 times daily
MuGard®	510k 062795	89109-0108-01	Benzalkonium Chloride, Benzyl Alcohol, Carbopol 971P, Polysorbate 60, Phosphoric acid	Chemical mouth rinse used 6 times daily for pain reduction
Caphosol®	510k 030802	08489-8000-01	Sodium Phosphate, Calcium Chloride	Chemical mouth rinse as saliva replacement therapy for dry mouth, use more than 6 times daily
Gelclair®	510k 013056	24477-0010-15	Sodium Hyaluronate	Chemical mouth rinse used 6 times daily to palliate pain
Kepivance®	NDA 125103	55513-520-06	Epithelial Cell Growth Factor	Intravenous growth factor not approved for Grade I & 2 mucositis; can be use once; has many adverse reactions.

### Savings with ProThelial™ In the U.S.

On average ProThelial™ reduces the cost of poorly managed mucositis by \$10,000 to \$27,000 per patient per course of chemotherapy treatment. Similarly, in patients receiving radiation therapy alone or with chemotherapy, ProThelial™ reduces costs by \$10,646 to \$24,660. By eliminating mucositis in stem cell transplant patients, ProThelial™ reduces costs by \$38,000 per transplant. Given that the incidence of poorly managed mucositis in the U.S. is approximately 400,000 patients annually, ProThelial™ brings in significant cost savings currently borne by insurers.

## Distinctions between ProThelial™ and Other Interventions

The distinctions between ProThelial™ and other interventions are shown in **Table 7** and **Table 8**. Mucositis interventions are delineated according to active ingredients, mechanisms of action and comparative clinical outcomes.

**TABLE 8. Comparative Therapeutic Outcomes (On-Label and Off-Label)**

Product	Mucositis Pain Reduction	Prevent Grade 3,4 Mucositis	Prevent Grade 1,2 Mucositis	Simultaneously Treats Grade 1,2,3,4 Mucositis	Complete Ulcer Pain Elimination	Full Mucosal Restoration
ProThelial™	Yes	Yes	Yes	Yes	Yes	Yes
Episil®	Yes	No	No	No	No	No
MuGard®	Yes	No	No	No	No	No
Caphosol®	Yes	No	No	No	No	No
Gelclair®	Yes	No	No	No	No	No
Kepivance®	Yes	Partially	No	No	No	No

## CONCLUSION

Mucositis is a serious, dose-limiting consequence of chemo-radiation in cancer treatment patients. Painful ulcers and erythema directly challenge alimentation with most patients requiring unplanned breaks in therapy, developing dehydration, poor caloric intake, subsequent weight loss and diminished chances for survival [64]. Among all mucositis interventions, ProThelial™ has the most to offer with several clinical features (**Table 9**) not seen in other approved anti-mucositis therapies. **First**, PCLS is fast, effecting complete reversal of signs and symptoms of mucositis within 2- 3 days. **Second**, when patients are instructed by oncologists to swish and swallow, ProThelial™ appears useful for both OM and GIM, simultaneously. **Third**, the treatment effect of ProThelial™ is wider in scope than other agents. It eliminates pain (lessening dependence on narcotic analgesia), restores normal oral mucosa, and restores upper GI function with swallowing and the ability to tolerate solids and liquids. This feature alone permits patients to self-maintain their nutritional status while undergoing cancer treatment. Additionally, in these patients, ProThelial™ minimized nausea and small intestinal cramping and it eliminated frequent loose movements in patients suffering from chemotherapy-induced diarrhea. **Fourth**, ProThelial™ seems useful to manage mucositis caused by a variety of oncologic agents, each having differing mechanisms of action - radiation, 5-fluorouracil, folinic acid, irinotecan, oxaliplatin, paclitaxel, carboplatin, cetuximab, ipilimumab and nivolumab. **Fifth**, PCLS was well-tolerated by all with no

**Table 9. Clinical Features of ProThelial™**

<ul style="list-style-type: none"> <li>• FDA Cleared Medical Device for Management of Oral Mucositis</li> <li>• Polymerized Cross-linked Sucralfate (Enhanced Potency Permitting Reduced Dosing)</li> <li>• Prevention of Oral Mucositis</li> <li>• Reversal of Oral Mucositis</li> <li>• Elimination of pain due to mucositis</li> <li>• Rapid 2-3 Day Onset of Completed Clinical Effect</li> <li>• †† Prevention of Alimentary (Gastrointestinal) Mucositis</li> <li>• †† Reversal of Alimentary (Gastrointestinal) Mucositis</li> <li>• †† Potential as a Single Agent Approach to Managing Oral &amp; Alimentary Mucositis</li> </ul>
†† Practitioner-discovered off-label therapeutic feature

patient-reported side effects. Of course, sucralfate, the active ingredient of ProThelial™, has an acceptable safety profile. **Sixth**, ProThelial™ is a singular agent with an acceptable means of administration, dosed at a frequency that is not cumbersome.

### Expert Commentary

Of the current mucositis interventions and those in development, the author recommends interventions that meaningfully impact the course of mucositis. Most interventions mitigate, lessen or palliate the symptoms and signs of oral mucositis. Presently approved oral rinses momentarily palliate or mask mucositis discomfort without reliably reversing or preventing the incidence.

Intravenous keratinocyte growth factor (Kepivance®) achieves a 30-40 basis-point reduction in the incidence of severe oral mucositis, which is indeed significant. However neither it nor other agents can completely prevent oral mucositis, or rapidly reverse all grades of mucositis as does ProThelial™. Additionally, ProThelial™ has an off-label therapeutic efficacy for mucositis in the small bowel and colon, rapidly reversing these symptoms and signs as well.

Once fully integrated in the clinical practice, the impact of ProThelial™ on this disease will be significant, as it will minimize or potentially eliminate a major cause of dose reductions and unplanned treatment interruptions in cancer treatment patients. Thus ProThelial™ may heighten patients' chances of receiving superior treatment outcomes, the doses of chemo-radiation being uncompromised.

ProThelial™ may allow patients to maintain a higher quality of life not otherwise available to a cancer treatment patient suffering from mucositis. Finally, by eliminating or significantly

minimizing oral mucositis, ProThelial™ will deliver superior health economic outcomes by lowering the cost of mucositis care by tens of thousands of dollars per patient per bout of mucositis.

**Table 10. Other Mucositis Interventions Under Development**

Company	Agent for US Market	Phase and Year	Mucositis Effect	Complete Reversal All Grades of Mucositis	Complete Prevention All Grades of Mucositis
Daewoong Pharma	rhEGF Spray	Phase II, 2014	Reduces Grade 3,4 from 31% to 13%	No	No
Sucampo Pharma	Cobiprostone Oral Spray	Phase Ia, 2013	Nonspecific	No	No
Soligenix	SGX942 – 5amino acid Peptide IDR (IV drug)	Phase II/III, 2014	Reduces Grade 3,4 By unknown extent	No	No
Cellceutix (PolyMedix)	Brilacidin, defensin-mimetic antibiotic Oral Rinse	Preclinical/Phase I 2014	Reduced Grade 3,4 by 90% in animal models	No	No
Actogenix	AG013-Bacteria as an oral rinse, that secretes a protein in the oral cavity	Proof of Concept, 2009	Reduces Grade 3,4 by 35%	No	No
Alder Pharma	Anti-IL-6 Antibody as an IV Drug	Phase I, abandoned	Reduces Grade 3,4 by 34%	No	No
Avaxia Biologic	Anti-TNF Antibody as an Oral Rinse/Topical	Phase 1, 2009	To be tested in Hamsters	No	No
Canopus Biopharma	Oltipraz as Oral Rinse	Phase II, 2009	"Prevents some severe forms of mucositis"	No	No
NephRx Corp	NX002-peptide derived from AMP-18 a growth factor	Proof of Concept, 2011	Demonstrated undisclosed efficacy	No	No
IndUS Pharma (Applied Protein Sciences)	Peptide with TGF biological activity, oral and intravenous	Phase 1, 2013	45% Reduction in Grade 3,4 mucositis	No	No

## Five Year View

In five years the field is likely to see the introduction of several other interventions for mucositis. Unfortunately, if knowledge of their current efficacy is a guide, these therapies are not likely to challenge the superior clinical outcomes achieved by ProThelial™. That said, the area of therapeutics for the oral mucositis is quite active with no less than 10 agents in various stages of development (**Table 10**).

All agents demonstrate some mitigating effects on the most severe forms of mucositis, with treatment effects that are 30-45 basis points better than placebo or control. Many have been in development for more than four years. However, none of the agents completely reverse all grades of mucositis and none completely prevent mucositis as does ProThelial™.

These pipeline candidates include two agents that are antibodies against pro-inflammatory cytokines, IL-6 and TNF (tumor necrosis factor). Three agents are peptides that mimic biological activities of anti-inflammatory cytokines, like growth factor. Two agents are novel applications of small molecules, cobiprostone and oltipraz. One is a new antibiotic (brilacidin), one is mucosa-adherent bacteria that secretes a cytoprotective protein, while yet another is a 5-amino acid peptide targeting the innate defense system against toxic effects of chemo-radiation. All candidates have compelling mechanisms of actions, but with treatment effects that are only 30-40 basis points better than placebo. ProThelial™, on the other hand, has treatment effects that are tens of thousand basis points better than placebo. Oncologists achieving superior clinical effects from ProThelial™ are not likely to surrender its use to candidates that are currently in the pipeline. The manufacturer of ProThelial™ is developing a drug indication use for this medical device.

**KK, Freidank A, Brennan MT, Bowen J, Dennis K, Lalla RV.** Systemic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the

### **Disclosure**

The author was responsible for the content, outline and arrangement of the manuscript. The author is an employee of Mueller Medical International LLC and owns stock.

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**Key Issues**

- Mucositis is a painful debilitating consequence of chemotherapy and radiation.
- Mucositis limits therapeutic dosing, creates unplanned treatment interruptions and thereby decreases cancer survival.
- Mucositis lowers the patients' quality of life, erodes their ability to eat and drink, directly contributing to weight loss and the need of artificial tube feeding.
- Current mucositis interventions – mouth rinses, biological agents, physical treatments – do not prevent or reverse mucositis once established.
- ProThelial™ is the most recently cleared medical device for the management of mucositis, containing polymerized cross-linked sucralfate that maintains a hyper-concentration of sucralfate three hours post-administration that is 800% higher than standard sucralfate on normal lining and 2400% higher on ulcerated lining.
- ProThelial™ rapidly reverses oral mucositis as well as completely prevents it, thus averting the customary use of prophylactic gastrostomy tubes in high-risk patients.
- ProThelial™ rapidly reverses mucositis of the esophagus, small bowel and colon.
- Higher ProThelial™ dosing of 1,000mg per dose may be required for some patients who incompletely respond to the lower standard doses of 250mg-500mg per dose.
- ProThelial™ can be used in the pediatric mucositis patients.
- By eliminating the impact of mucositis, ProThelial™ reduces costs of care by \$10,000 to \$27,000 per patient per episode of oral and gastrointestinal mucositis.

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