**STUDY TITLE**

**The use of thermoresponsive, mucoadhesive solgels in post endoscopic sinus surgery cavities**

**Confidential**

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**Statement of Compliance**

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

1. **General information**

Title: The use of thermoresponsive, mucoadhesive solgels in post endoscopic sinus surgery cavities

1. **Investigator details**

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1. **Research sites**

The Princess Alexandra Hospital

199 Ipswich Road, Woolloongabba, Brisbane, 3176 2111

Greenslopes Hospital

Newdegate Street, Greenslopes, Brisbane 3394 7111

1. **Rationale & background information**

Chronic rhinosinusitis (CRS) is a heterogeneous, multifactorial disease defined by sinonasal inflammation persisting for more than 12 weeks. According to the Australian National Health Survey, in 2007-2008, 9.2% of the Australian population reported to suffer from CRS. Along with sinonasal symptoms, patients also frequently suffer with low mood, poor sleep and fatigue leading to significant direct and indirect costs to the health system. Despite the prevalence of the condition in the community and the burden both physically and financially, there is an ongoing search for an efficient and practical method to deliver ongoing treatment.

The recent International Consensus Statement on the treatment of CRS include nasal saline irrigation and intranasal corticosteroid sprays/drops with the addition of a short course of oral corticosteroids for the CRS with nasal polyps (CRSwNP) subgroup(1). Topical therapy offers the benefits of high local concentrations without the systemic side effects, however in unoperated sinuses, delivery to the sinus mucosa is limited and less than 2% of the irrigated volume reaches the sinuses(2). Endoscopic sinus surgery (ESS) is essential to allow topical treatment to effectively reach the sinus cavities and is the treatment of choice in patients who fail to respond to appropriate medical therapy (AMT). The intention of ESS is to restore natural sinus ventilation and drainage pathways, relieve nasal obstruction with the preservation of mucosa, and ultimately allow CRS treatment to be de-escalated from systemic to topical treatments for long-term management.

Topical corticosteroids are an integral component of postoperative care in ESS and managing the inflammatory component of the disease. There is high-level evidence supporting their use, which has been shown to significantly improve patient’s self-reported symptoms and endoscopic scores at 6 and 12 months. In the clinical setting, steroids are mixed into high volume washes for delivery. Unfortunately, these devices have short mucosal contact time, are wasteful and require daily use. An ideal drug preparation should be delivered in a manner to optimise mucosal contact time with steady absorption and minimal wastage(3).

There has been considerable interest in the potential of mucoadhesive, thermoresponsive in situ gelling systems (soluble gels) as a potential vector for drug delivery. These polymer-based gels can be formulated to rapidly transform in situ from a liquid to gel once at sinonasal temperature and slowly release a drug to the target tissue. Recently, these soluble gels have been analysed ex-vivo in human nasal tissue and demonstrated prolonged mucosal contact time and sustained release of dexamethasone (4). Establishing the viability of these gels in-vivo potentially opens an innovative method for drug delivery to the sinonasal mucosa with the potential to treat a broad range of conditions, including CRS.

This aim of this trial is to assess the use of solgels as a vector to deliver medications, specifically dexamethasone in surgically opened sinus cavities. Assessment of delivery to individual sinuses, residence time and local side effects will be the primary areas of interest.

**References**

1. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. International Forum of Allergy and Rhinology. 2016 Feb;6 Suppl 1(S1):S22–09.

2. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, Chusakul S, Praweswararat P. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? American Journal of Rhinology. OceanSide Publications, Inc; 2008 Sep 1;22(5):483–6.

3. Harvey RJ, Schlosser RJ. Local drug delivery. Otolaryngol Clin North Am. 2009 Oct;42(5):829–45–ix.

4. Pandey P, Cabot PJ, Wallwork B, Panizza BJ. Formulation, functional evaluation and ex vivo performance of thermoresponsive soluble gels-A platform for therapeutic delivery to mucosal sinus tissue. European Journal of …. 2017;96:499–507.

1. **Study goals and objectives**

The goal of this study is to assess whether solgels may have the potential to be used to deliver dexamethasone and in the future other drugs to the paranasal sinuses following functional endoscopic sinus surgery. The delivery technique, residence time and side effects profile will be assessed. The objective is to determine the length of time the solgel remains within a postoperative sinus cavity and wether there are any side effects. Secondary objectives will be to establish if there is any therapeutic benefit in patients with diseased cavities.

1. **Study Design**
   1. Prospective, interventional trial
   2. 10 participants
   3. Inclusion criteria
      1. Above 18 years of age
      2. Currently fit and healthy
      3. Available for required follow up
      4. Previous endoscopic sinus surgery >6 weeks ago
   4. Exclusion criteria
      1. Allergies to any of the medications being used in the trial
   5. Expected duration of study
      1. 2 months

1. **Methodology**

The study involves the application of a solgel containing dexamethasone to previously opened sinus cavities. The solgel will be prepared at the Princess Alexandra Hospital in the Pharmacy department using techniques described by Pandey et al(4) with blue food dye added to aid contrast between mucosal tissue.

Participants will be recruited from Greenslopes Private hospital from the two supervising consultants outpatients. They will be eligible if they are at least 6 weeks or more post endoscopic sinus surgery and had at least either their maxillary or ethmoid sinuses opened surgically. They will be approached at their postoperative follow up appointment by the treating consultant. If they are interested in participating in the trial will be contacted by the primary investigator to discuss the trial and obtain consent.

The trial will be conducted at the Princess Alexandra Hospital in the ENT Outpatient department. Each participant will receive three actuations (100 micrograms/actuation) of Co-phenylcaine nasal spray (ENT Technologies, Melbourne) to each nostril to anaesthetise and decongest the nasal cavity prior to solgel administration. Under direct vision using a rigid endoscope (Storz), solgel will be applied to the surgically opened sinus cavities of the maxilla and/or ethmoid and/or sphenoid sinus using a syringe device. A photo will be taken before and after the solgel application.

The maxillary sinus and/or sphenoid cavity will have 2 ml of solgel applied to the posterior wall while the ethmoid cavity will have 1ml applied. The cavities will be assessed again in 5 minutes with the rigid endoscope to assess the distribution. The patient will then be reviewed the following day and have their sinuses re-examined to assess for remaining gel. If the gel is still present, they will be reviewed again at day 5 to assess for the presence of the solgel.

Patients with diseased sinuses will have their sinuses graded independently by a sinus surgeon using the Modified Lund Mackay postoperative endoscopy score if they are assessed at the day 5 visit to assess for any improvement.

1. **Safety Considerations**

An adverse event is any untoward medical occurrence in a participant or clinical investigation participant, temporarily associated with the procedure or therapy, whether or not considered related to the procedure or therapy.

The patient will receive a max dose of 1mg of dexamethasone topically in a slow release preparation, which is significantly lower than toxic doses used for this medication and the dose used in intravenous dosing guidelines. Even if the release were instantaneous, the dose would be similar to other corticosteroids used on a daily basis to treat paranasal disease.

All excipients including poloxomer 407, polycarbophil and polyvinyl alcohol are approved for use by the Food and Drug Administration (FDA) and will be used in FDA approved concentrations. Poloxamer 407 is commonly used in intranasal preparations including decongestants. Polycarbophil is used in mucosally applied preparations including to buccal, nasal, ophthalmic, vaginal, and rectal mucosa and is also used as a controlled release polymer in oral solid dose applications. Polyvinyl alcohol is a water soluble polymer that is used widely as a carrier polymer in drug delivery systems such as sustained-release particles and hydrogels. Polyvinyl alcohol hydrogel is also used as a drug delivery device for mucosally applied preparations such as for rectal administration of indomethacin.

Patients will be assessed and screened for side-effects and have the opportunity to report any further side effects during the initial administration, clinic follow up and via correspondence in the week following the trial. Potential side effects include headaches, nasal irritation and nose bleeds.

1. **Follow-Up**

The patients will be followed up for one week following the completion of the study to monitor for any side effects. They have contact details to report any adverse events during this time.

1. **Data Management and Statistical Analysis**

All data will be stored on an encrypted drive as de-identified data. Patients will be allocated a trial number and the information stored under that number. The only time personal information will be collected is on the consent form.

1. **Expected Outcomes of the Study**

Our goal is to establish the performance of solgels in the sinus cavities, which potentially opens a new and exciting vector for drug delivery and has the potential to treat a broad range of pathologies and deliver a variety of medications of the sinonasal mucosa. We suspect there will be minimal side effects associated with the solgel given the components involved and our earlier work within the nasal cavity.

1. **Dissemination of Results and Publication Policy**

The trial protocol will be registered in the clinical trials database <https://clinicaltrials.gov/> prior to the commencement and upon completion the results will be made available to the public through this site and through submission to a relevant medical journal.

1. **Duration of the Project**

The study is expected to take 2 months following Ethics approval to complete.

1. **Ethics**

This clinical trial will be registered on the Clinical Trials.gov website found at <https://clinicaltrials.gov/> prior to commencement of patient recruitment.

This study has been submitted to the Metro South Human Research Ethics Committee

1. **Informed Consent Forms**

The participants will be given an information sheet with an outline of the trial, inclusion and exclusion criteria and information about adverse event follow up and risk. They will be given time to consider the trial and any further questions they have will be answered. They will then sign a consent form before participating in the trial.

1. **Financial disclosure and conflicts of interest**

The Investigators declare no conflicts of interest

1. **Curriculum Vitae of investigators**

Please See Attached.